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Department of Health
and Human Services

Abstracts of Small Business Innovation Research (SBIR) Phase I and Phase II Projects

COMPLETED

Fiscal Year 1987

Department of Health
and Human Services

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of
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PREFACE

Public Law 97-219, the Small Business Innovation Development Act of 1982, was passed by Congress and signed by the President in order to increase the role of small businesses in federally supported research and development. This legislation created the Small Business Innovation Research (SBIR) Program, involving 11 federal agencies, of which the Department of Health and Human Services (DHHS) is the second largest participant. Within the Department, the National Institutes of Health (NIH) account for 92% of the SBIR activity. In 1986, the statute was extended by the enactment of Public Law 99-443, which authorizes the continuation of the SBIR Program through 1993.

The SBIR Program consists of three phases. Phase I awards are generally $50,000 for a period of approximately six months and are intended for technical feasibility studies. Phase II, considered the principal research and development phase, is to continue the research effort initiated in Phase I. Awards for Phase II are made for periods of 1 to 3 years for amounts normally not to exceed $500,000. Only Phase I recipients are eligible to seek Phase II support. In Phase III, the small business is to pursue, with private capital, the commercialization of the results of the research funded in Phases I and II.

In FY 87, the fifth year of the SBIR Program, the DHHS made a total of 590 SBIR awards, 357 of which were for Phase I efforts and 233 for Phase II projects. These awards, which included grants, contracts, and cooperative agreements, totaled $67.2 million, with funding from NIH accounting for $61.6 million of the total amount.

Awards are made on the basis of scientific and technical merit, with consideration given also to program relevance, potential for commercial applications, and availability of funds.

The abstracts in this publication are organized by funding agency within DHHS and by awarding component within each agency (where appropriate). The abstracts appear in the following order: Phase I grants, Phase II grants, Phase I contracts, and Phase II contracts. The Office of Human Development Services is the only component of DHHS that uses neither grants nor contracts. The abstracts within this section are for projects supported by cooperative agreements.

Names, addresses, telephone numbers, and principal investigators of the awardee organizations are provided for those who may wish to contact these companies for additional information.

NATIONAL INSTITUTE ON AGiNG

Phase I Grants

Title of Project: Effects of a Health and Well-Being Program on the Elderly
Principal Investigator: Helaine Alessio, Ph.D.
Awardee Organization: Adults Health & Development Programs, Inc.
2007 Pelden Road
Adelphi, MD 20783
Telephone Number: (301) 431-3733
Awardee Number: 1 R43 AG05018-01A1

The hypothesis to be tested is that a 7-day, health and well-being camp (Adults Health & Development Programs, Inc.'s Camp AHDP) for the "well" elderly will significantly improve objective and subjective health, symptomatology, subjective well-being, and aspects of physical fitness.

The approximately 80 participants will be independently living, relatively healthy adults between ages 50 to 90 years. They will be randomly divided into two groups: an experimental group to receive the Camp AHDP experience and a control group that will not. Each group will be randomly divided into half to receive follow-up telephone calls to determine the effect of a reinforcing call on health behavior. Measures will be obtained 1 week prior to the camp, and 1 day, 1 month, and 3 months after the camp ends. Preliminary data suggest that the camp positively affects the variables of interest in this project.

If data indicate that the research design is feasible, Phase II will (1) extend the research to a larger sample incorporating more rigorous control, and (2) develop Camp AHDP on a national basis. The latter will involve collaboration with other organizations that serve the "well," the "infirm" elderly, and the Hispanic elderly.

Title of Project: Fall-Event Recording System
Principal Investigator: John F. Gray
Awardee Organization: ANCO Engineers, Inc.
9937 Jefferson Boulevard
Culver City, CA 90232-3591
Telephone Number: (213) 204-5050
Awardee Number: 1 R43 AG07213-01

To further biomedical and clinical research into the aging process, a video-recording system permitting the generation of a video data library of fall events is needed.

This proposal delineates the functional requirements of a video-recording system that would automatically record fall events. Its unique features will include the ability to record the entire event, including the circumstances and happenings just prior to the fall. Two alternative methods of fall sensing are proposed, their applicability being dependent upon the location monitored. If desired, the system can be configured to alert personnel at remote locations that a fall has occurred so they may respond appropriately to the emergency.

Title of Project: Imaging of Elements in Tissue at Trace Concentrations
Principal Investigator: Norbert Thonnard, Ph.D.
Awardee Organization: Atom Sciences, Inc.
114 Ridgeway Center
Oak Ridge, TN 37830
Telephone Number: (615) 483-1113
Awardee Number: 1 R43 AG07197-01

Instrumentation enabling quantitative trace element-concentration imaging with high sensitivity and resolution (1 ppm, 5μm) of biological tissue sections over 2×2 mm^2 would be a valuable research tool. Simultaneous structural imaging would enhance its utility. Sputter-Initiated Resonance Ionization Spectroscopy (SIRIS) will be adapted to provide structural imaging and quantitative element-concentration imaging of biological tissue sections. The method will be tested by imaging the concentrations of iron and aluminum in tissue sections from brains of Alzheimer's disease victims and correlating these images with surface structures visible in secondary electron images from the identical location. Optical microscopy of adjacent stained sections will also be performed.

SIRIS utilizes a focused ion beam to sputter neutral atoms and ions from the sample surface. The ions are rejected, while the neutral atoms are ionized with narrow-band lasers tuned to specific transitions of the selected element. This yields a uniformly high ionization efficiency for any selected element, with essentially no ionization or interference from other constituents in the sample. Imaging will be implemented by rastering the ion beam over the sample with synchronous detection, storage, and display of the secondary electron and SIRIS ion signals. The system will also be applicable to the semiconductor industry, surface science, and geoscience.

Title of Project: Urinary Incontinence Treatment System for Home Nursing
Principal Investigator: John D. Perry, Ph.D.
Awardee Organization: Biotechnologies, Inc.
P.O. Box 256
Bryn Mawr, PA 19010
Telephone Number: (215) 525-8778
Awardee Number: 1 R43 AG06755-01

This project will develop an inexpensive, portable EMG biofeedback instrument to aid in the treatment of urinary incontinence in women and men. This instrument will monitor, evaluate, and count voluntary exercise contractions of the pubococcygeus muscle in order to assure patient compliance with nursing instructions, and to assure more efficient patterns of therapeutic intervention in the restoration of urinary control. Coupled with inexpensive, single-user EMG sensors, the instrument's criterion-defined feedback, compactness, portability, and low cost will enhance the usefulness of the instrument as a practical alternative treatment, especially (but not exclusively) for the growing numbers of elderly incontinent.

The design features of the instrument are intended to promote the adoption of effective training protocols for independent home use, to reduce the need for frequent office or clinic reassessment. Use of the device will aid in minimizing the role of incontinence as a determining factor in admissions to nursing home facilities and will reduce the costs of incontinence for individuals currently residing in nursing homes. Phase I will investigate and progressively refine the essential design parameters of the device. In Phase II, appropriate clinical testing will be conducted to refine a maximally useful home healthcare device.

Title of Project: Computerized Memory Training for the Elderly
Principal Investigator: Javaid I. Sheikh, M.D.
Awardee Organization: Decision Systems
1473 Miramonte, Building 2
Los Altos, CA 94022
Telephone Number: (415) 323-1105
Awardee Number: 1 R43 AG06753-01

In Phase I, Decision Systems proposes to develop a prototype computertized memory training package named MemoryPerfect. It is designed to teach a variety of relaxation, imagery, and mnemonic techniques that research shows improves recall of information in the elderly.

The MemoryPerfect prototype consists of six modules. The first is the Records-Keeping Module, which maintains a running score of the user's performance, returns the user to the training module last used, and maintains and displays a chart of the training modules completed and those yet to be studied. The second module is the Manus and Command Line Prompts Module. Third is the Introductory Session Module, and fourth is the Anxiety Evaluation and Relaxation Training Module, which assesses the user's degree of learning anxiety and offers relaxation training if necessary. The fifth module is the Imagery Pretraining Module, used to improve the user's ability to create effective images during memory training. The final module is the Mnemonic Training Module, used to teach a wide variety of memory improvement techniques.

Decision Systems has identified the following vertical markets for the computerized training: (1) senior citizen centers, (2) retirement community recreational centers, (3) audio-visual centers at public libraries, and (4) medical care centers.

Title of Project: Eccentric Contractions Effects on Musculoskeletal Aging
Principal Investigator: Keith M. Johnston
Awardee Organization: Design/Analysis Services Company
4001-32 Northwest 43rd Street
Gainesville, FL 32607
Telephone Number: (904) 392-4251
Awardee Number: 1 R43 AG07203-01

Osteoporosis, degenerative joint disease, and primary muscle atrophy are three age-related disorders of the musculoskeletal system. Osteoporosis affects 90 percent of women over 75 years, osteoarthritis afflicts 80 percent, and muscle atrophy is progressive with age. Physical conditioning retards bone loss, stabilizes deteriorated joints, and prevents muscle atrophy. The most efficient stimulus to produce these effects is therapy utilizing submaximal eccentric muscle contraction. Exercise of this type generates an equivalent training effect with less energy expenditure and less cardiovascular stress.

There are presently no isotonic eccentric devices available to study exercise in which the resistance in the lifting phase of the cycle can be different from the resistance during the lowering phase. Phase I will involve development of a mechanism with which eccentric muscle conditioning can be performed. The application of the principles learned from this project may increase function and activity for postsurgical patients, neurologically impaired individuals, and the elderly.

National Institutes of Health
National Institute on Aging

Title of Project: A Physical Activity Questionnaire for Use with Older Adults
Principal Investigator: Richard A. Washburn
Awardee Organization: New England Research Institute, Inc.
42 Pleasant Street
Watertown, MA 02172
Telephone Number: (617) 923-7747
Awardee Number: 1 R43 AG07199-01

The physical activity questionnaire is the most practical and widely used approach for the assessment of physical activity in epidemiological research. However, physical activity questionnaires specific to older individuals have not been developed. Valid and reliable techniques for the assessment of physical activity in older populations are needed before the risks and benefits associated with participation can be adequately evaluated.

The aim of this research is to develop a prototype questionnaire for the assessment of physical activity in individuals age 60 and over. Existing items for assessing the major dimensions of physical activity will be modified and expanded. Following a careful evaluation by the investigators and a panel of experts, the final prototype will undergo a limited field evaluation. The final product will be a prototype activity questionnaire for use in older populations that will be refined and developed during Phase II. A questionnaire of this type will be a valuable research tool for both epidemiological and clinical research on the role of physical activity and health in the elderly.

Phase II Grants

Title of Project: Devices for Automatic Detection of Urination
Principal Investigator: Otakar Jonas
Awardee Organization: Jonas, Inc.
1113 Faun Road
Wilmington, DE 19803
Telephone Number: (302) 478-1375
Awardee Number: 2 R44 AG05095-02A1

The objectives of this proposal are to field test two prototype devices for qualitative detection of urination (one for personal use, one with a remote alert) and to complete development and laboratory and field testing of a prototype device for quantitative urine detection. The qualitative device, an inexpensive disposable undergarment for use in home or geriatric care institutions, utilizes an automatic detection and alarm system for alerting the patient or attendant at a remote station. The quantitative device will use special disposable undergarments and will be used after surgery and as a research tool.

During Phase I, the qualitative detection devices were developed and successfully tested in the laboratory. During Phase II, batch quantities will be manufactured and field tested at cooperating geriatric care institutions. The quantitative detection device was designed in Phase I; it will be completed, batch manufactured, and laboratory and field tested during Phase II. These devices will be useful for improving personal health care, reducing skin problems, helping in internal treatments and surgical procedures, and providing research data.

The commercial applications are extensive, potentially helping up to one million incontinent individuals in the United States. All three devices will reduce health care costs to individuals, institutions, insurance companies, and the United States government.

Title of Project: Respite Care for Frail Older Adults: A Prototype
Principal Investigator: Joan Brogdon
Awardee Organization: Kin Care, Inc.
1000 West Diversey Parkway
Chicago, IL 60614
Telephone Number: (312) 975-7777
Awardee Number: 2 R44 AG05464-02

This research is to implement, further refine, and evaluate a prototype foster care model to provide short-term, overnight care to frail older adults in private residences. Appropriate community care utilization can ease caregiver burden and stress and decrease the likelihood of institutionalization. One undeveloped service option is short-term, overnight, community-based respite care within private residences. The anticipated outcome will be an effective, self-sustaining, marketable service that can be replicated by either proprietary or not-for-profit agencies for frail older adults and other dependent populations.

Data are expected to support the ability of private individuals to implement a training program generalized from behavioral approaches and nursing care concepts, enabling them to function as surrogate caregivers. Caregiver burden and stress is expected to be relieved. Frail older adults who utilize the service are expected to maintain their living statuses longer than would be expected by chance. Financial data are expected to support Kin Care's ability to function independently in the third year and licensure recommendations will be developed.

A pre/posttest design with follow-up utilizing a nonequivalent comparison group and survey techniques will be implemented. Eighty older adults and 40 caregivers will comprise the main sample and will be followed over a period of 1 year. Data analysis will utilize descriptive and inferential statistics, including Anova, Manova, Logit, and Probit procedures.

Title of Project: New Derivatization Reagents and Methods for the Analysis of Bioactive Amines
Principal Investigator: Osborne S. Wong
Awardee Organization: Oread Laboratories, Inc.
2065 Constant Avenue
Lawrence, KS 66046
Telephone Number: (913) 749-0034
Awardee Number: 2 R44 AG06271-02

The objective of this project is to develop a selective and sensitive method for the trace analysis of bioactive amines in biological matrices. The methodology exploits the use of fluorogenic derivatization because many biogenic amines, such as amino acids and peptides, lack the physicochemical properties that would allow their quantification at physiologically relevant levels. The novel technology is derived from the ability of primary amines to form fluorescent isoindole-type derivatives in the presence of aromatic dicarboxaldehydes and appropriate nucleophiles. Relative to the current methods of primary amine analysis, the newly discovered assay offers improved sensitivity and product stability, and greater versatility.

Long-range goals of this program include: (1) the design and synthesis of new, effective dicarboxaldehydes, (2) the exploration of new, superior nucleophiles, (3) the evaluation of the potential of benz(f)isoindole as an effective chemiluminescence emitter, (4) the optimization of reaction conditions for biologically important amines, and (5) the development of assays for biogenic amine analysis. The technology to be developed is essential for the research and development of peptide- and protein-based products in the biotechnology and pharmaceutical industries, and in the detection of bioactive amines in biomedical research and diagnostic laboratories.

Title of Project: Lipid-Incorporated, Serum-Free Medium
Principal Investigator: Menashi Cohenford, Ph.D.
Awardee Organization: Scott Laboratories, Inc.
771 Main Street
West Warick, RI 02893
Telephone Number: (401) 828-5250
Awardee Number: 2 R44 AG06273-02

The long-term goal of this project is to design a serum-free, chemically defined medium (CDM) for optimum growth of mammalian cells *in vitro*. Lipids play a critical role in the growth and normal development of cells. However, they are insoluble and have been introduced in media either in complex with carrier proteins or in unstable inclusions known as liposomes, rendering the media undefined.

During Phase I, lipids were covalently bound to a highly hydrophilic polymer with repeating monomeric subunits. They were found to become soluble, stable, and chemically defined. The conjugates exhibited biological activity and stimulated proliferation, attachment, and collagen expression in COLO 357, a human pancreatic cell line.

In Phase II, polymer-bound lipids will be synthesized in pilot scale, and their effects on proliferation, attachment, and product expression will be evaluated in Chinese hamster ovary cells, bovine kidney cells, Vero, and mouse SP-2 hybridoma cells. Growth will be monitored microscopically and by ^{3}H-thymidine uptake assays. ^{3}H-leucine will be used to quantitate protein synthesis. Antibody production and viral replication will be quantitated by ELISA. A serum-free CDM will substantially simplify the isolation and purification of mammalian cell products in culture.

Title of Project: Morbidity Risk Assessment in the Elderly
Principal Investigator: Ben T. Williams, M.D.
Awardee Organization: University Park Pathology Associates, P.C.
1408 West University Avenue
Urbana, IL 61801
Telephone Number: (217) 367-3645
Awardee Number: 2 R44 AG06021-02

University Park Pathology Associates, P.C. plans to design, implement, and test a health-risk assessment computer program that generates estimates of the probability of hospitalization, disability, and other adverse health outcomes as a function of medical history, laboratory findings, and health habits. The program will be used in conjunction with health examination/screening programs for persons aged 60 and above in order to recommend appropriate interventions for risk reduction.

Phase II involves refining the rough model specified in Phase I to allow for inclusion of emerging research findings through development of a knowledge-based expert system to guide decisions about inclusions and quantification of new risk factors, testing the prototype model for validity and client acceptability, and documenting the delivery program and expert system capabilities for program expansion.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Phase I Grants

Title of Project: Measurement of Interleukin-2 and Interleukin-2 Receptor by ELISA
Principal Investigator: Vali Kermani-Arab, Ph.D.
Awardee Organization: Advanced Allergy Research Centers, Inc.
10642 Santa Monica Boulevard, Suite 102
Los Angeles, CA 90025
Telephone Number: (213) 474-6063
Awardee Number: 1 R43 AI24041-01A1

During the past 20 years, different biological activities have been described for lymphokines produced by activated leukocytes. Interleukin-1 (IL-1) is a factor produced by activated mononuclear phagocytes and is essential for supporting both T-cell and B-cell responses. Activated T cells produce interleukin-2 (IL-2), a factor necessary for T-cell proliferation. This soluble factor exerts its biological effects by interacting with specific high-affinity receptors on the surface of activated T cells. A decrease in the ability to produce IL-2 and dysfunction of interleukin-2 receptors (IL-2Rs) have been found in several diseases, including autoimmunity, graft versus host rejection, acquired immune deficiency, lymphoadenopathy, and cancer. Thus a strong rationale exists for the investigation of IL-2 and IL-2R.

Phase I of this study will develop a sensitive ELISA assay for the measurement of IL-2 and IL-2R in the same sample of cultured lymphocytes; determine the optimal conditions for the assay; and determine the sensitivity of the assay by comparison with a bioassay. Phase II will involve the measurement of IL-2 and IL-2R in normal subjects and in patients with cancer, AIDS, arthritis, SLE, and pemphigus, as well as in transplantation subjects and others. When sufficient clinical data have been accumulated, the assay will be converted into kit form for research and clinical use.

Title of Project: Iontophoretic Catheter Research
Principal Investigator: Gene L. Mrava
Awardee Organization: Advanced Clinical Products, Inc.
10817 Trade Road
Richmond, VA 23236
Telephone Number: (804) 794-9744
Awardee Number: 1 R43 AI24850-01

The urinary tract is a major site of nosocomial infections. The leading cause of these infections is urinary catheterization, which in turn is the most common predisposing factor for fatal gram-negative sepsis in hospitals. The long-term objective of iontophoretic catheter research is to develop a device to prevent catheter-related urinary tract infections.

The ultimate configuration envisioned consists of a specially designed Foley-style catheter containing two metal electrodes within the drainage lumen. Provision is made for connecting the electrode leads to a microampere constant current power supply. The catheter is thus modified for iontophoresis application. Preliminary microbiological testing shows that noble metal iontophoresis can kill various bacterial genera.

The research proposed in this Phase I study is directed at determining feasibility of this concept by (1) a complete screening test consisting of parametric evaluation of potential electrode materials, several bacterial genera, and levels of electromotive force; (2) the conduct of electrode reliability/survival evaluation in a suitable medium; and (3) the design and fabrication of a urodynamic evaluation system for subsequent evaluation in the dynamic fluid flow mode.

Title of Project: Cryoimmunoassay: Ice Nucleation as a High-Gain Detector
Principal Investigator: Paul K. Wolber, Ph.D.
Awardee Organization: Advanced Genetic Sciences, Inc.
6701 San Pablo Avenue
Oakland, CA 94608
Telephone Number: (415) 547-2395
Awardee Number: 1 R43 AI24817-01

Advanced Genetic Sciences, Inc. proposes the potential use of bacterial ice nuclei as a high-sensitivity, low-background detector for clinical immunoassays. This system could be adapted to current immunoassays, reducing sample sizes needed for accurate immunodetection. Ice nuclei could also be used to construct new assays for immunodetection of viruses, rickettsia, and bacteria, without previous biological amplification.

The specific goals of this proposal are to demonstrate coupling of ice nuclei to an immune recognition event, discover appropriate chemistries for covalent linkage of ice nuclei to antibodies and/or biotin, and construct a working immunoassay for alpha-fetoprotein, an important marker for detection of certain cancers. The alpha-fetoprotein assay will be compared in sensitivity and accuracy to existing assays based upon radioisotopic or enzymatic detection. The research makes use of standard immunological and biochemical techniques, as well as ice nuclei heterologously expressed in *E. coli*, after cloning of an ice nucleation gene from *P. syringae*. If successful, this detection system could provide to many assay systems sensitivities previously attainable only via biological amplification.

Title of Project: Synthetic Vaccines Utilizing Baculovirus Polyhedra
Principal Investigator: Elliot Rosen, Ph.D.
Awardee Organization: American Biogenetic Sciences, Inc.
P.O. Box 1001
Notre Dame, IN 46556
Telephone Number: (219) 239-5295
Awardee Number: 1 R43 AI24371-01

The aim of this proposal is the adaptation of baculovirus for the production of synthetic vaccines. Late after infection, baculovirus-infected cells produce paracrystalline occlusion bodies that consist primarily of a single protein, polyhedrin.

American Biogenetic Sciences, Inc. intends to modify the polyhedrin gene of *Autographa californica* to generate recombinant occlusion bodies exposing antigenic determinants of pathogenic microorganisms. This requires (1) identifying the appropriate regions of the polyhedrin in which to insert sequences encoding new antigenic determinants, (2) constructing recombinant polyhedrin genes *in vitro*, (3) transferring the recombinant genes into the baculovirus genome, (4) expressing the hybrid gene and generating recombinant occlusion bodies, and (5) characterizing new epitopes expressed on the recombinant crystal. Antigenic determinants of well-characterized proteins will be used to demonstrate the feasibility of the technique. Later, antigenic determinants of pathogens will be expressed.

The system offers several potential advantages, including the high level of expression of the baculovirus expression system, the ease of purification of occlusion bodies, and their production in a system free of human pathogens. In addition, the occlusion bodies are large structures; this should enhance the immunogenicity of the exposed epitopes and permit the presentation of many copies of the antigenic determinant.

Title of Project: Quantification of Basophil-Histamine Release by EIA
Principal Investigator: Wai-Sai Ma, Ph.D.
Awardee Organization: Animal Biotech Corporation
1531 Monrovia Avenue
Newport Beach, CA 92663
Telephone Number: (714) 645-2111
Awardee Number: 1 R43 AI24408-01

Histamine is an important biochemical mediator that causes allergic symptoms. IgE molecules have a high affinity for receptors on basophils. The presence of specific allergens will bridge IgE bound on basophil and initiate a chain of events leading to histamine release. Quantifying basophil-histamine release essentially measures the cell-bound, allergen-specific IgE and will allow evaluation of a patient's allergic status. Results indicate the patient's biological active-cell sensitivity to allergens. The test may be used to: (1) identify specific allergies of patients, (2) suggest initial safe dosages of immunotherapy, (3) monitor progress of immunotherapy, and (4) estimate allergenic extract potency.

Phase I studies seek to develop a procedure to release histamine from sensitized basophils under control conditions and an immunoassay to quantitate histamine by enzyme immunoassay (EIA) techniques. Polyclonal antibody specific to histamine has been developed. Animal Biotech Corporation will affinity-purify the antihistamine antibody and conjugate the enzyme horseradish peroxidase (HRPO) to the antibody. The amount of histamine in a sample will be measured by the inhibition of antihistamine-HRPO binding to microtiter-well histamine. Phase II will include all the clinical studies to correlate data with the skin test, RAST, and monitor progress of immunotherapy.

Title of Project: Electromicrofiltration for Monoclonal Antibody Recovery
Principal Investigator: John M. Radovich, Ph.D.
Awardee Organization: Bend Research, Inc.
64550 Research Road
Bend, OR 97701-8599
Telephone Number: (503) 382-4100
Awardee Number: 1 R43 AI24851-01

In the near future, sustained production of large (kg) quantities of monoclonal antibodies (MAB) will be required for therapeutic applications and medical diagnostics. Membrane processes are well suited to processing large volumes of culture fluid for recovery of protein products. The long-term objective of the proposed research is to develop an effective and economical membrane process for the continuous recovery of MAB from suspension cultures of hybridoma cells.

The specific aims of the proposed Phase I research are to demonstrate the feasibility of applying electromicrofiltration (EMF) to the recovery of MAB from mouse hybridoma cell cultures and to determine the principal factors that govern efficiency of the EMF process. To achieve this goal, a highly porous, nonfouling microporous membrane will be selected to use in an EMF test cell. Parametric and long-term studies will be conducted to determine the effect of the electric field on the membrane flux and MAB recovery. A Phase II program would focus on optimizing the properties of the microporous membrane and the operating conditions for EMF and on developing a prototype system.

Title of Project: Soluble MHC Molecules to Induce Allograft Tolerance
Principal Investigator: Richard A. Flavell, Ph.D.
Awardee Organization: Biogen Research Corporation
14 Cambridge Center
Cambridge, MA 02142
Telephone Number: (617) 864-8900
Awardee Number: 1 R43 AI24990-01

Polymorphic cell-surface molecules encoded by the major histocompatibility complex (MHC) of vertebrates are responsible for initiating a number of physiological responses when these antigens are recognized as "nonself" by the immune system. The rejection of donor tissue grafts by recipients whose MHC molecules are dissimilar presents a major obstacle in the field of transplantation.

While attempts to help individuals tolerate these cell-surface antigens have met with considerable difficulty, the ease of inducing tolerance to soluble nonself proteins has been firmly established. Thus, Biogen Research Corporation proposes to genetically engineer these MHC molecules to be expressed as secreted forms so they can be purified easily. The ability of these molecules to experimentally induce tolerance to allografts in mice will be investigated in Phase II studies. If successful, these methods can be applied to the human system.

Title of Project: Rapid, Accurate Identification of Gram-Positive Organisms
Principal Investigator: Barry R. Bochner, Ph.D.
Awardee Organization: Biolog, Inc.
3447 Investment Boulevard, Suite 3
Hayward, CA 94545
Telephone Number: (415) 785-2564
Awardee Number: 1 R43 AI22762-01A1

Gram-positive bacteria are responsible for a major portion of bacterial infections. Although some species in this group are easily identified, better general identification methods are needed. It is expected that Biolog, Inc.'s new technology will permit identification of the commonly addressed gram-positive organisms as well as rapid and accurate identification of less common gram-positive bacteria that frequently cause serious infection in compromised hosts. Existing products cannot adequately identify these organisms.

Biolog, Inc. holds two patents on a new redox method of testing that can be developed into identification tests for all clinically important microorganisms. These tests will identify an organism based on patterns of carbon source utilization. The method employs a tetrazolium dye to colorimetrically indicate carbon source oxidation.

This Phase I study will demonstrate the feasibility of developing a rapid and accurate speciation kit for gram-positive bacteria. Two tasks are involved: (1) the development of a suspension medium compatible with the redox chemistry that is tailored to this group of organisms, and (2) a survey of approximately 200 organic chemicals to demonstrate that new and useful speciation tests can be found. Biolog, Inc.'s technology offers many advantages over present technologies, including speed, simplicity, and accuracy.

Title of Project: Online Directory of Immunoclones and Their Immunoreactive Products
Principal Investigator: Donna R. Maglott, Ph.D.
Awardee Organization: Bioresources Laboratories, Inc.
12301 Parklawn Drive
Rockville, MD 20852
Telephone Number: (301) 881-2600
Awardee Number: 1 R43 AI24829-01

The technology of producing hybridomas and other cloned cell lines that secrete immunoreactive substances, such as monoclonal antibodies, is now commanding attention in all fields of biology. The wide applicability of monoclonal antibodies as highly specific reagents and the increasing number of investigators working with monoclonals necessitate a centralized information resource containing descriptions of hybridomas and product availability.

The Hybridoma Data Bank (HDB) has been organized by the International Council of Scientific Unions as a cost-sharing project. Funding is provided by various government agencies and organizations representing the many disciplines encompassed by hybridoma technology. Because of the size, scope, and complexity of the HDB, it cannot be accessed online. Questions are submitted by mail or telephone to be handled by data bank staff. These information professionals perform the required research and mail reports to the requestors.

This project is to create an online directory to the HDB on the Dialcom Network. This menu-driven system, updated monthly, will contain basic data on available hybridomas, monoclonal antibodies, and other immunoreactive products of cloned cell lines. Users will be able to access the system from almost any country in the world through public communication networks. They will be able to order products online directly from vendors and request further information about products listed in the directory.

Title of Project: Ethylthioribose: A New Antifungal Agent
Principal Investigator: Adolph J. Ferro, Ph.D.
Awardee Organization: Epitope, Inc.
15425-E Southwest Koll Parkway
Beaverton, OR 97006
Telephone Number: (503) 641-6115
Awardee Number: 1 R43 AI24382-01

The incidence of fungal infections has increased markedly since the advent of broad-spectrum antibiotics, corticosteroids, cancer chemotherapy, and organ transplantation. Currently available antifungal agents such as amphotericin B are often avoided clinically because of their severe toxic side effects (e.g., nephrotoxicity). Epitope, Inc. has synthesized ethylthioribose (ETR), a water-soluble, acid-stable analog of the naturally occurring compound methylthioribose. In preliminary experiments, ETR has been found to: (1) be cytocidal to *Candida albicans in vitro*, (2) have no effect on the growth of mammalian cells *in vitro*, and (3) have no apparent adverse effects on mice when administered intraperitoneally or intravenously.

The long-term objective is to develop effective and nontoxic antifungal/antimicrobial agents. The specific aims of this phase of the project are to: (1) determine the *in vivo* efficacy of ETR in a mouse model of systemic candidiasis, (2) determine the toxicity of ETR in mice, and (3) determine the antimicrobial spectrum of ETR against a wide variety of clinical isolates. The development of a nontoxic antifungal agent will allow early therapeutic intervention in patients with suspected fungal infections as well as prophylactic treatment in immunocompromised patients.

Title of Project: Photo Cross-Linkable DNA Oligonucleotide Probe to HTLV-III
Principal Investigator: George D. Cimino, Ph.D.
Awardee Organization: HRI Research, Inc.
2315 Fifth Street
Berkeley, CA 94710
Telephone Number: (415) 548-2999
Awardee Number: 1 R43 AI25294-01

A psoralen-monoadducted, cross-linkable DNA oligonucleotide probe to a conserved portion of the HTLV-III genome will be prepared and used in an innovative hybridization assay. The assay is conducted at the melting temperature of the respective probe-target hybrid using high concentrations of probe. Hybridization and photochemical fixation are carried out concurrently over a period of minutes after which excess probe is removed by a denaturing wash step. The sensitivity and ease of use of this probe will be compared to an otherwise identical unmodified probe used in a traditional blot format. RNA isolated from HTLV-III-infected cell cultures will be used as the target sequence in these assays.

Favorable results will justify assays on actual clinical specimens using novel nonradioactive amplification schemes. The resultant test for HTLV-III could serve as a model for additional tests for other infectious and genetic diseases.

Title of Project: Rapid Detection System for HTLV-III
Principal Investigator: Nicholas Giorgio, Ph.D.
Awardee Organization: ImClone Systems, Inc.
180 Varick Street
New York, NY 10014
Telephone Number: (212) 645-1405
Awardee Number: 1 R43 AI24824-01

ImClone Systems, Inc. seeks to develop a novel rapid detection system for the identification of antibodies directed against human T-cell lymphotropic virus III (HTLV-III). The system is based on a sandwich fluoro-immunoassay in which an HTLV-III antibody containing serum sample is premixed with fluoresceinated HTLV-III viral antigen conjugate and subsequently allowed to incubate with an optical grade fiber to which HTLV-III viral antigens have been covalently attached.

Accumulation of the fluoresceined HTLV-III viral antigens on the fiber surface provides a localized concentration of fluorescein which is excited by electromagnetic radiation in the visible wavelength range of 490 nm. Emission of fluorescein at 525 nm is recaptured by the fiber and propagated to the end where it is collected and detected as a light signal output. This system has the potential to become a sensitive, rapid detection assay with simplified sample handling, small sample requirements, and wide use in numerous clinical settings including physicians' offices, clinical laboratories, and blood banks.

Title of Project: Antigenicity of Gonococcal Pilus Oligomers
Principal Investigator: John C. McMichael, Ph.D.
Awardee Organization: ImmunoMed Corporation
5910-G Breckenridge Parkway
Tampa, FL 33610
Telephone Number: (813) 621-9447
Awardee Number: 1 R43 AI24380-01

The development of a safe and efficacious vaccine for gonorrhea based on oligomers from pili is a major goal of ImmunoMed Corporation. Early attempts to develop gonorrhea vaccines using intact pili failed because of antigenic diversity among the bacterial strains in the population. A preliminary study of oligomers from the type 2 colonial form of *Neisseria gonorrhoeae* has shown that they were better than intact pili for eliciting antibodies that cross-react with pili from heterologous strains. This result suggests that a vaccine containing oligomers should provide better cross-protection than one containing intact pili.

In this proposal, antibodies elicited by oligomers from up to 10 strains of *Neiserria gonorrhoeae* will be examined to (1) confirm their capacity for cross-reactivity with intact pili from heterologous strains, and (2) determine their capacity for preventing bacterial adhesion to human cells. If a significant advantage for the use of oligomers is indicated, a Phase II application would be made for the development of a prototype gonorrhea vaccine based on those strains yielding oligomers with the greatest degree of cross-reactivity.

Title of Project: A Homogeneous Assay for Hepatitis B Virus Surface Antigen
Principal Investigator: Bruce Babbitt, Ph.D.
Awardee Organization: Liposome Sciences, Inc.
c/o Department of Biochemistry
University of Tennessee
Knoxville, TN 37996-0840
Telephone Number: (615) 974-4015
Awardee Number: 1 R43 AI24816-01

Target-sensitive immunoliposomes will be prepared by using monoclonal antibody to the hepatitis B virus surface antigen. The liposomes will spontaneously lyse upon binding with antigen particles in serum, thereby releasing the entrapped signal enzymes. Liposome Sciences, Inc. expects to show that the new assay is completely homogeneous (requiring no washing or separation steps), rapid (within 90 minutes), and sensitive (detecting as little as 0.5 ng antigen/ml in unprocessed serum).

Title of Project: Production of Reference Reagents for SAIDS and STLV-III
Principal Investigator: David A. Fuccillo, Ph.D.
Awardee Organization: Microbiological Associates, Inc.
5221 River Road
Bethesda, MD 20816
Telephone Number: (301) 654-3400
Awardee Number: 1 R43 AI24384-01

Two distinct, virally induced infections in nonhuman primates that cause substantial morbidity and mortality and have clinical relevance to the human AIDS virus have been identified recently. The first, designated SAIDS, is caused by a variety of closely related Type D viruses. The second is induced by a lentivirus, which is morphologically, biologically, and serologically related to human HTLV-III and HTLV-IV and is designated STLV-III. These viruses are important because they: (a) infect many nonhuman primates and may have major effects on experimentation in these species and (b) can serve as potential models for examining the biology, pathogenesis, and potential therapy of AIDS-like diseases.

Microbiological Associates, Inc. proposes to grow isolates of the SAIDS viruses (SRV-1 and SRV-2) in Raji cells and the STLV-III virus in HUT-78 cells. Standardized reagents (i.e., virally infected cells, homologous antisera from infected monkeys, and heterologous antisera from rabbits immunized with whole virus isolates) would be characterized. These reagents could then be used to develop assays for the rapid identification of animals exposed to the virus.

Title of Project: DNA Probes for the Diagnosis of Bacterial Vaginosis
Principal Investigator: Diana K. Sheiness, Ph.D.
Awardee Organization: MicroProbe Corporation
1725 220th Street, Southeast, #104
Bothell, WA 98021
Telephone Number: (206) 485-8566
Awardee Number: 1 R43 AI25257-01

The role of five bacteria and a mycoplasma as the etiologic agents of bacterial vaginosis (BV) is supported by growing scientific data. Standard methods are inadequate for the routine diagnosis of this disease. Eight hundred to 1,000 nucleotides of the 16S ribosomal RNA (rRNA) of each BV microorganism will be sequenced. Short DNA probes will be synthesized to detect the 16S rRNA of each BV microorganism. ^{32}P-labeled DNA probes will be hybridized against high-molecular-weight RNA and DNA isolated from individual pure cultures. Hybridization specificity of each DNA probe will be evaluated in tetraethylammonium chloride and tetramethylammonium chloride solutions to abolish the preferential melting of A-T versus G-C base pairs in DNA hybrids, yielding hybridizations that are only chain-length dependent. In these solutions, mixtures of probes of the same length, but differing in sequence, will exhibit identical hybridization properties.

These salt solutions will also allow simultaneous use of multiple probes (of the same length) and will allow the development of a universal hybridization format. The long-term objective is to provide a rapid and accurate diagnostic test for BV.

Title of Project: Synthetic Oligonucleotides for Trypanosome Chemotherapy
Principal Investigator: Dennis E. Schwartz, Ph.D.
Awardee Organization: MicroProbe Corporation
1725 220th Street, Southeast #104
Bothell, WA 98021
Telephone Number: (206) 485-8566
Awardee Number: 1 R43 AI25266-01

The 5′ ends of all trypanosome mRNAs have recently been shown to have a common 35-nucleotide spliced leader (SL). The SL is believed to arise by transcription within a mini-exon-derived RNA (medRNA) of about 140 nucleotides, followed by its trans-splicing with the primary transcripts of mRNAs.

The presence of the SL in all trypanosomal mRNAs provides an ideal system to test the efficacy of short oligonucleotides as therapeutic agents. Synthetic oligonucleotides, consisting of diesters, ethyl phosphotriesters, or methyl phosphonates, will be synthesized. These will be complementary to the SL sequence or to the splice-donor site of the medRNA to directly inhibit protein synthesis or mRNA maturation. These oligonucleotides will be tested for their ability to inhibit protein synthesis in cell-free systems using purified mRNA, and in cell cultures of *Trypanosoma brucei*. Specific antisense oligonucleotides will provide valuable chemotherapeutic agents for the treatment of significant human diseases.

Title of Project: Rapid Detection of Chlamydia Antigen
Principal Investigator: Anne L. Bailey
Awardee Organization: Photec Diagnostics, Inc.
101 East Main Street
Little Falls, NJ 07424
Telephone Number: (201) 890-1258
Awardee Number: 1 R43 AI24379-01

With the rapid rise of chlamydial trachomatis infections to an epidemic state of three to ten million cases per year, there is significant need for a rapid infection detection method that can be inexpensively performed on smears from clinical specimens. Prior to 1983, the diagnosis of this disease was expensive and time consuming, as the preferred method was isolation in tissue culture. Two new diagnostic methods, enzyme immunoassay and immunofluorescent assays, are presently commercially available but lack ease and speed of performance, as they require highly trained individuals and expensive instrumentation.

Photec Diagnostics, Inc. has developed a novel assay which is rapid, inexpensive, and easy to perform. Presently this methodology has been applied to a sandwich Apoprotein A-1 test, which utilizes a tablet containing a covalently bound capture antibody and a dye-labeled antibody. Photec has developed dye polymer labels which can potentially increase the sensitivity of the procedure tested with Apoprotein A-1 to the level needed for chlamydia antigen. The combination of dye polymer labels and a tableted solid phase support which spontaneously settles in the reaction tube allows the development of inexpensive, rapid diagnostic tests which can be read in "tube" photometers.

Title of Project: An *Haemophilus* OMP as a Vaccine Candidate
Principal Investigator: Bruce A. Green, Ph.D.
Awardee Organization: Praxis Biologics, Inc.
30 Corporate Woods, Suite 300
Rochester, NY 14623
Telephone Number: (716) 272-7000
Awardee Number: 1 R43 AI25233-01

Vaccination is the most cost-effective means of preventing *Haemophilus influenzae* type b (Hib) disease. Newly developed Hib polysaccharide-protein conjugate vaccines being tested are effective in children 2 months and older. However, some infants may not be able to respond to polysaccharide antigens. A 15,000 dalton peptidoglycan-associated lipoprotein (PAL), identified as a potential vaccine candidate, has been found in all Hib isolates tested. In addition, it is antigenically conserved among Hib strains. The 15K PAL constitutes 1.5 percent of the total OMPs, making it difficult and expensive to purify commercially. These studies will facilitate production of large amounts of the protein for use as a vaccine. This would be the first use of a protein vaccine against Hib disease.

These studies will use recombinant plasmids that encode the putative 15K-PAL gene in *Escherichia coli* to overexpress the gene product, under the control of a regulatable promoter. Immunogenicity of the cloned protein will be examined using both bactericidal assays and animal protection studies. Phase II studies will develop procedures amenable to large-scale purification of the cloned protein and additional immunogenicity testing.

Title of Project: Oral Malaria Vaccine Development in a *Plasmodium berghei* Model
Principal Investigator: Robert N. Brey III, Ph.D.
Awardee Organization: Praxis Biologics
30 Corporate Woods, Suite 300
Rochester, NY 14623
Telephone Number: (716) 272-7000
Awardee Number: 1 R43 AI25232-01

Peptide carrier and recombinant DNA-produced *Plasmodium falciparum* sporozoite subunit vaccines have been tested in clinical trials. These vaccines have been designed to induce high-titer protective antisporozoite antibodies. Clinical trials have indicated that these vaccines are only partly effective. Recent studies compared analogous peptide and recombinant subunit vaccines with sporozoite-induced immunity in the *Plasmodium berghei* model. These studies showed that parenterally administered *P. berghei* subunit vaccines induce high-titer sporozoite antibody that is partially protective at low-sporozoite challenge doses. In contrast, sporozoite-induced immunity, fully protective at 20 times the challenge, is mediated by cellular immunity.

These Phase I studies are designed to examine the feasibility of immunizing mice against *P. berghei* sporozoites, a rodent malaria parasite, by oral vaccination. Vaccination of mice with an attenuated *Salmonella* strain harboring plasmids that direct the extracytoplasmic localization of the *P. berghei* circumsporozoite protein (CS) is expected to elicit not only antibody-mediated but also cell-mediated immune responses. The *P. berghei* CS gene will be fused to the gene encoding the B subunit of the heat-labile enterotoxin of *E. coli* (LTB) at various locations, and the fusion protein will be tested for immunogenicity. If these studies are successful, analogous oral malaria vaccines could be developed for humans.

Title of Project: Monoclonal Antibody Test Kit for *Campylobacter*
Principal Investigator: Patrick F. Coleman, Ph.D
Awardee Organization: Synbiotics Corporation
11011 Via Frontera
San Diego, CA 92127
Telephone Number: (619) 451-3770
Awardee Number: 1 R43 AI24413-01A1

Acute gastroenteritis may be the second most common illness in humans, with *Campylobacter* among the most important causative agents. Worldwide, there are a billion cases of diarrhea annually and several million deaths. There are no licensed or widely used rapid diagnostic methods available to identify *Campylobacter* infection. When used, the stool culture is arguably the most untimely and cost ineffective of all the microbiological tests. Synbiotics Corporation's goal is to develop monoclonal antibody-based tests, useful in conventional formats, which can detect *Campylobacter* infections.

In Phase I, monoclonal antibodies reactive with the serotypes pathogenic in humans will be produced. These will be tested in EIA assays for sensitivity and specificity against the host cell line, likely confounding cell lines and viral or bacterial strains, and stool samples.

In Phase II, these monoclonal antibodies or antibodies from sister clones will be adapted to other formats to satisfy the needs of the diverse market segments. Complete, convenient systems will be developed around these kits, each giving results comparable to those obtained with culture; clinical trials for all will be conducted.

Title of Project: Monoclonal Antibody Test Kit for Rotavirus
Principal Investigator: Patrick F. Coleman, Ph.D.
Awardee Organization: Synbiotics Corporation
11011 Via Frontera
San Diego, CA 92127
Telephone Number: (619) 451-3770
Awardee Number: 1 R43 AI24400-01

Acute gastroenteritis is one of the most common afflictions in humans, with human rotaviruses among the most important causative agents. These pathogens account for 40 to 60 percent of the diagnosed cases of pediatric (under age 2) gastroenteritis and are the single most important etiologic agent for acute gastroenteritis in the developed countries. In the less developed countries, rotavirus is the third most commonly detected pathogen. Presently, diagnosis is developed from results of EM identification (impractical in many settings), ELISA assays (impractical for small numbers of specimens, prone to false positives), or emerging latex assays. This proposal is to develop monoclonal antibodies that can be employed in a variety of test formats.

In Phase I, Synbiotics Corporation will produce monoclonal antibodies reactive with the four serotypes pathogenic in humans. These will be tested in EIA assays for sensitivity and specificity against ATCC cell lines, likely confounding cell lines and viral or bacterial strains, and characterized stool samples. In Phase II, these antibodies will be adapted to latex or solid phase immunoassay kits to provide end products suitable for various situations. Results obtained with these kits will be comparable to those obtained with the EIA test format. Clinical trials will then be conducted.

Title of Project: Improved Reagents for Syphilis Diagnosis
Principal Investigator: Alan Walfield
Awardee Organization: Syntro Corporation
10655 Sorrento Valley Road
San Diego, CA 92121
Telephone Number: (619) 453-4000
Awardee Number: 1 R43 AI24411-01

A project to develop a state-of-the-art serodiagnostic assay for syphilis with recombinant *Treponema pallidum* antigens is proposed. The development of recombinant DNA-derived reagents would be of great benefit to the public health agencies, clinical labs, hospitals, and blood banks that conduct serodiagnostic tests for syphilis by improving accuracy and lowering the costs of testing. The antigens would be proteins reliably and inexpensively produced from bacteria bearing chimeric DNA. They would readily lend themselves to inclusion in automated diagnostic systems and one-day testing in doctors' offices.

Syntro Corporation proposes to purify antigens expressed by *E. coli-T. pallidum* recombinant plasmids and evaluate them as serodiagnostic reagents in an experimental immunoassay system. This would test the feasibility of a recombinant DNA approach. Additionally, it is proposed to explore whether or not these antigens would best be provided by a chimeric-DNA expression vector other than *E. coli*.

National Institutes of Health
National Institute of Allergy and Infectious Diseases

Title of Project: Cloning and Expression of Human Interleukin-3
Principal Investigator: Frederick S. Hagen, Ph.D.
Awardee Organization: ZymoGenetics, Inc.
2121 North 35th Street
Seattle, WA 98103
Telephone Number: (206) 632-4036
Awardee Number: 1 R43 AI23212-01A1

The goal of this project is to develop a commercially feasible system for the production of the human equivalent of interleukin-3 (IL-3) for use as a therapeutic agent in the treatment of patients whose hematopoiesis has been suppressed as a result of chemotherapy or radiation therapy, or who are recovering from bone marrow transplantation.

In Phase I, cDNA will be cloned into a GEM-1 *in vitro* transcription vector. A plasmid library will be established in *E. coli*. After replica plating, plasmid DNA will be prepared from subsets of the library and linearized with restriction endonucleases. RNA will be transcribed from the cDNA in each pool using SP6 or T7 RNA polymerase. The RNA pools will be translated in frog oocytes. Expression of IL-3 will be assessed by tissue culture biological assays. Those library subsets which produce IL-3 activity will be further subdivided until pure clones of IL-3 are isolated. Expression of biologically active IL-3 in Phase I will provide information for determining the feasibility of obtaining production level expression in Phase II. Future research will involve scale-up of production and purification of IL-3 to commercial levels and performance of trials to determine safety, dosage, and usefulness of the drug.

Phase II Grants

Title of Project: New Biologics to Prevent Swine TGE and Pseudorabies
Principal Investigator: Gregory B. Wilson, Ph.D.
Awardee Organization: Amtron, Inc.
701 East Bay Street
Charleston, SC 29403
Telephone Number: (803) 577-2931
Awardee Number: 9 R44 AI24438-02

Amtron, Inc. will undertake production and testing leading to U.S. Department of Agriculture (USDA) approval of two Immunity Inducers (official name designated by USDA) to prevent the occurrence of transmissible gastroenteritis (TGE) and pseudorabies virus (PrV) in newborn pigs. The development of Immunity Inducers stems from advanced research in immunomodulators in Phase I, which has enabled the company to demonstrate the feasibility of harvesting large quantities of immunomodulators specific to the diseases in question (and numerous others) without harm to the source animals.

The process of producing TGE and PrV Immunity Inducers will be further defined and clinically tested in this project in conjunction with outside contractors, and sufficient serials of each product will be produced to meet USDA guidelines for commercial application of these biologic products. This project will require a minimum of 15 months to complete and should result in USDA approval for commercial use of these products, both of which will significantly improve swine production because of the present absence of efficacious TGE and PrV vaccines that can induce immunity during the first few days of life in piglets. The production objective of this project will be half a million doses of Immunity Inducers for both diseases.

Title of Project: Development of Protease-Deficient, Gram-Positive Host
Principal Investigator: Peter Blackburn, Ph.D.
Awardee Organization: Applied Microbiology, Inc.
#5 Brooklyn Navy Yard
Brooklyn, NY 11205
Telephone Number: (718) 852-5353
Awardee Number: 2 R44 AI23561-02

Applied Microbiology, Inc. (AMBI) has been developing *Bacillus subtilis* and related species as a host system for the production of recombinant protein products. *B. subtilis* has several advantages over *E. coli* (e.g., it secretes protein products, is nonpathogenic, and does not produce endotoxins). AMBI has previously inactivated the alkaline and neutral protease (AP and NP) genes of *B. subtilis*. Work done under the Phase I proposal identified and characterized the residual proteases, that together account for all remaining extracellular protease activity in the AP/NP strains constructed at AMBI. Under the Phase II proposal, AMBI will clone and inactivate the residual protease genes to produce a host free of extracellular protease activity. A means of expressing recombinant products throughout growth and in stationary cultures by the use of appropriate promoters will also be developed. This will greatly increase product yield in protease free hosts. In addition, a method to produce accurately processed recombinant proteins in *B. subtilis* will be determined.

Title of Project: Rapid, Accurate Identification of Non-Fermenters (NEGNB)
Principal Investigator: Barry R. Bochner, Ph.D.
Awardee Organization: Biolog, Inc.
3447 Investment Boulevard, Suite 3
Hayward, CA 94545
Telephone Number: (415) 785-2564
Awardee Number: 2 R44 AI22761-02

Approximately 15 percent of bacterial infections are caused by nonenteric gram-negative bacilli (NEGNB), an extremely heterogeneous group of bacteria. Commercially available NEGNB identification kits often yield ambiguous results, requiring additional tests which are slow and costly.

Biolog, Inc. holds two patents on a new redox method of testing which can be developed into identification tests for virtually all clinically important microorganisms. The tests will be extremely accurate, easy to perform (one-step inoculation, one-color read-out), and rapid (less than 4 hours). The proposed product will speciate the NEGNB based on a panel of carbon source oxidation tests. Testing is performed in microtiter plates and employs a tetrazolium dye used in Biolog, Inc.'s patented chemistry to colorimetrically indicate carbon source oxidation.

In Phase I, 29 species and 36 strains were tested against 200 carbon sources. A feasible 16-test prototype kit was demonstrated that could distinguish each of the 29 species from all the other 28 by a minimum of 3 traits. In Phase II, the survey will be automated and expanded to include 83 species, 5,000 strains, and 400 carbon sources. From the results of this study, we expect to finalize a prototype NEGNB Identification Kit and evaluate it in a collaborative clinical study.

Title of Project: Genetic Engineering Approaches to AIDS Vaccines
Principal Investigator: Paul A. Luciw, Ph.D.
Awardee Organization: Chiron Corporation
4560 Horton Street
Emeryville, CA 94608
Telephone Number: (415) 655-8729
Awardee Number: 2 R44 AI22778-02

The main objective of this proposal is to utilize genetic engineering methodologies to develop a safe and effective subunit vaccine for preventing infection by the AIDS (acquired immune deficiency syndrome) retrovirus. AIDS and ARC (AIDS-related complex) are significant causes of morbidity and mortality in the United States and on the African continent. Currently, no effective treatment for limiting disease or inhibiting the AIDS retrovirus exists.

This proposal will investigate immunological properties of viral antigens expressed in genetically engineered yeast and mammalian cells; similar expression vectors are being utilized for the production of other vaccines (e.g., hepatitis B virus) and for production of enzymes and hormones for therapeutic use in humans. The research effort on the AIDS system in this proposal will contribute to understanding both basic aspects of pathogenesis and fundamental mechanisms of immunity.

Title of Project: Viscosin and Related Analogs as Therapeutics for Chagas' Disease
Principal Investigator: Terrence Burke, Ph.D.
Awardee Organization: Peptide Technologies Corporation
Box 368 Main
125 Michigan Avenue, Northeast
Washington, DC 20017
Telephone Number: (202) 234-3385
Awardee Number: 2 R44 AI23571-02

The antibiotic viscosin, a cyclic depsipeptide isolated from *Pseudomonas viscosa*, shows promising *in vitro* and *in vivo* (mice) cytotoxicity against *Trypanosoma cruzi*, the causative agent in Chagas' disease. The total synthesis of viscosin, undertaken in Phase I, will be completed to confirm its structure. The synthetic methods developed will then be used to prepare several analogs to determine structure-activity relationships. Work will be directed toward the development of a therapeutically useful and commercially accessible drug that can be used to treat Chagas' disease, which at present is an incurable and potentially fatal disease affecting millions of people.

Title of Project: Human Granulocyte-Macrophage Colony Stimulating Factor
Principal Investigator: Frederick S. Hagen, Ph.D.
Awardee Organization: ZymoGenetics, Inc.
2121 North 35th Street
Seattle, WA 98103
Telephone Number: (206) 632-4036
Awardee Number: 2 R44 AI22772-02A1

Human granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor that primarily stimulates the growth and development of granulocytes and macrophages and, of less certain significance, platelets and red blood cell precursors *in vitro*. GM-CSF has also been shown to have similar effects on hematopoiesis in primate model systems. This suggests a potential for clinical use in stimulating the more rapid return of white blood cell levels to normal in patients treated with chemotherapy.

Currently, a proprietary system for the production of GM-CSF in filamentous fungus is being used to produce GM-CSF. The efficacy of the native, carbohydrate-free GM-CSF produced in this system will be compared to rGM-CSF made by mammalian cells in a primate model system. This model system will be used to determine the role of carbohydrate in the circulatory half-life, antigenicity, toxicity, and efficacy of GM-CSF. Different portions of the amino acid sequence of GM-CSF will also be tested to determine whether a subset or altered-sequence form of GM-CSF may be developed that would be a more effective therapeutic agent. Expression of GM-CSF will be optimized to commercial production levels, and a large-scale purification scheme will be developed.

Phase I Contracts

Title of Project: Development of an ELISA Test for Antibodies to Human B-Lymphotrophic Virus

Principal Investigator: Anne J. Bodner, Ph.D.
Awardee Organization: Biotech Research Laboratories, Inc.
1600 East Gude Drive
Rockville, MD 20850
Telephone Number: (301) 251-0800
Awardee Number: 1 N43 AI72675-00

NIH researchers have recently announced the isolation of a human B-lymphotropic virus (HBLV) from six individuals with various lymphoproliferative and immune disorders. HBLV appears to belong to the group of human herpes viruses and may be associated with B-lymphoproliferative disorders. Early serological tests using indirect immunofluorescence methods revealed that only 4 of 220 random, healthy blood donors were seropositive for HBLV antibodies. More recent reports state that the prevalence of HBLV infection may be higher. An ELISA-based assay for HBLV antibody detection would facilitate further study of the prevalence of infection with this virus and the relation of infection to human disease.

HBLV has been seen to be infectious in several cell lines as well as in fresh B lymphocytes. In this proposal, Biotech Research Laboratories, Inc. presents its plan for using HBLV cultured in the HSB-2 cell line to demonstrate the feasibility of developing an ELISA-based test kit for HBLV antibody detection.

Title of Project: Development of Nonradioactive DNA Probes for the Detection of HBLV

Principal Investigator: Sandra K. Dusing-Swartz, Ph.D.
Awardee Organization: Biotech Research Laboratories, Inc.
1600 East Gude Drive
Rockville, MD 20850
Telephone Number: (301) 251-0800
Awardee Number: 1 N43 AI72669-00

A novel human B-lymphotropic virus (HBLV) has been recently isolated from patients with lymphoproliferative disorders. This herpes virus has been shown to infect B and T lymphocytes and to alter their morphology and growth characteristics. The significance of the virus in causing human diseases has not been fully evaluated but is certainly of much interest to researchers and clinicians.

Biotech Research Laboratories, Inc. has developed a rapid and sensitive assay for detection of HBLV-infected cells by *in situ* hybridization and for HBLV DNA in cell or serum extracts by slot blot hybridizations. The probe consists of a plasmid containing sequences coding for a portion of the HBLV genome chemically labeled with dinitrobenzene (DNB). Specific hybridization is detected by reactivity with rabbit anti-DNB followed by alkaline phosphatase-conjugated goat antirabbit IgG and color development. This hapten-labeled probe is a stable, sensitive, and specific alternative to the use of radiolabeled probes.

Eventually, the simplified HBLV DNA detection system will be assembled with all necessary components supplied in kit form for routine use in clinical laboratories. The availability of such an inexpensive and practical DNA probe kit for HBLV will facilitate the study of the etiological and epidemiological significance of this virus.

Title of Project: Development of a Rapid Immunoassay for Syphilis
Principal Investigator: Tsue-Ming Lin, Ph.D.
Awardee Organization: Diamedix Corporation
2140 North Miami Avenue
Miami, FL 33127
Telephone Number: (305) 324-2300
Awardee Number: 1 N43 AI72671-00

Syphilis, still a major serious infectious disease, can be treated effectively if diagnosed early. The number of deaths from syphilis in the United States has shown a steady decrease, but the number of syphilis cases has not shown a significant drop. Serological tests play a major role in the diagnosis of syphilis. These tests must be performed by qualified technicians in a laboratory. The proposed project is to develop a rapid, simple, reliable, and inexpensive immunoassay suitable for use in physicians' offices.

Antigens of the causative agent *Treponema pallidum* will be coated onto a filter paper as a small dot. In the assay, the test serum sample, enzyme-labeled antibodies to human immunoglobulins, and substrate are added sequentially to the antigen dot. No incubation is required, since the sample and reagents diffuse rapidly, contacting and reacting instantaneously with each other in the fiber mesh. The results are read visually, and a blue dot indicates a positive reaction.

The research will focus on: (1) selection of filter papers that will give a maximum coating of antigens but a minimum nonspecific adsorption of serum and reagents; (2) best conditions (temperature, time, buffer, and concentration) for coating antigens; (3) postcoating (materials and conditions) to minimize or eliminate background reaction; and (4) volume and concentration of sample and reagents. A refined assay procedure will be tested with a panel of more than 200 clinical serum samples.

Title of Project: Production of HLA Monoclonal Antibodies by B-Cell Lines
Principal Investigator: Myron J. Waxdal, Ph.D.
Awardee Organization: F.A.S.T. Systems, Inc.
4 Research Court
Rockville, MD 20850
Telephone Number: (301) 977-9291
Awardee Number: 1 N43 AI72668-00

Information generated in the past few years has begun to elucidate the genetic organization of the HLA complex at a molecular level using DNA and protein biochemistry methods. These studies indicate that multiple molecules in the form of heterodimers are expressed on the cell surface and that each heterodimer may carry several epitopes. These epitopes are, by analogy to the mouse, likely to be involved in cell-cell interactions. Likewise, these epitopes are likely to be involved in susceptibility to disease and important in matching for transplantation. Characterization of patients by protein and by DNA methods is not practical. Methods are time consuming, expensive, and not adapted to use in heterozygotes.

Identification of monoclonal antibodies against biologically relevant isotopes would have significant impact. Mouse antihuman monoclonal reagents recognize primarily monomorphic determinants with only a few recognizing polymorphic determinants. Human antihuman monoclonal antibodies offer the advantage of exquisite specificity but are not stable.

In Phase I, it is proposed to establish human B-cell lines transformed with Epstein-Barr virus that are producing antibody against epitopes on HLA-D region molecules and to determine the frequency with which reagents that define new subtypes are obtained. These new subtypes will be correlated with published studies on DNA polymorphism. These antibody-producing lines are stable and essentially monoclonal in nature.

Title of Project: Methods for Improving Expression of Transfected Immunoglobulin Genes
Principal Investigator: Marvin B. Hendricks, Ph.D.
Awardee Organization: Integrated Genetics, Inc.
31 New York Avenue
Framingham, MA 01701
Telephone Number: (617) 875-1336
Awardee Number: 1 N43 AI72667-00

The aim of this research proposal is to develop methods to improve the expression of transfected immunoglobulin (Ig) genes. The long-term goal is to improve the yield of genetically engineered antibodies of therapeutic value. Phase I will investigate two approaches to increase expression. One approach is to identify host myeloma cells that are more active in expressing transfected Ig genes; the other approach is to develop schemes to increase the number of gene copies that are expressed.

Phase II research will implement the findings of Phase I to formulate a methodology and set up experiments to express high levels of genetically modified antibodies. The research that is proposed here could lead to the production of genetically modified antibodies in yields comparable to that of highly productive myeloma or hybridoma cell lines. This would then make the production of genetically engineered antibodies a commercially feasible process.

Title of Project: Fast Clinical Immunovirology
Principal Investigator: Norman G. Anderson, Ph.D.
Awardee Organization: Large Scale Biology Corporation
7503 Standish Place
Rockville, MD 20855
Telephone Number: (301) 424-5989
Awardee Number: 1 N43 AI72672-00

The objectives of this project are to develop new and rapid methods for detecting, isolating, and characterizing new viruses, known virions, viral antigens, and antibodies to known pathogenic viruses. The methods to be explored depend on unique combinations of centrifugal techniques, and the banding densities and sedimentation coefficients of both individual species

of virus particles and of fluorescent and nonfluorescent latex particles. The methods include (in order of increased instrumentational complexity) density-separated fluorescent immunoaggregates, rate-separated fluorescent immunoaggregates, isopycnometric virus detection, and two-dimensional centrifugal virus isolation.

With these methods it is proposed that new viruses can be rapidly isolated and characterized; tests can be developed that will yield precise virus titers, allowing methods for growing the virus to be evaluated even when very poor yields are obtained; and rapid methods for diagnosis of viral diseases based on virion detection, antigen detection, or antibody detection can be developed. The principles of the methods will be studied in Phase I. In Phase II, a prototype will be developed and initial applications will be made.

Title of Project: Chemiluminescence Immunoassay for *Candida* Antigens
Principal Investigator: Ashok Patel, Ph.D.
Awardee Organization: London Diagnostics, Inc.
10300 Valley View Road, Suite 107
Eden Prairie, MN 55344
Telephone Number: (612) 941-3812
Awardee Number: 1 N43 AI72673-00

The aim of this project is to demonstrate an immunometric assay for *Candida* antigen (mannan) using acridinium esters as a chemiluminescent label. This will lead to a technique for the detection of fungal antigens that requires high sensitivity, by a method that is simpler, safer, and cheaper than conventional methods.

Monoclonal antibodies to *Candida* mannan will be purified and characterized for their usefulness in immunoassays. They will be covalently labeled with an acridinium ester to a high specific activity and used to develop a sensitive chemiluminescence assay. The assay will be optimized and compared to current methods.

The research should provide an assay for systemic *Candida* infection using stable reagents. The assay will demonstrate high specificity obtained by using monoclonal antibodies and sensitivity from the chemiluminescence technique. This will lead to Phase II research, development, and production of a commercial chemiluminescence assay, prototype instrument design and to clinical trials.

Title of Project: Monoclonal Antibodies to Human Parainfluenza Viruses 1 and 2
Principal Investigator: Ranjit Ray
Awardee Organization: Molecular Engineering Associates, Inc.
2126 7th Avenue South
Birmingham, AL 35233
Telephone Number: (205) 324-4887
Awardee Number: 1 N43 AI72674-00

Molecular Engineering Associates, Inc. proposes to develop a panel of monoclonal antibodies to human parainfluenza virus types 1 and 2. Antibodies will be evaluated by neutralization, hemagglutination inhibition, neuraminidase inhibition, fusion inhibition, ELISA, immune precipitation, Western blot, and immunofluorescence assays. The objective of the Phase I proposal is to identify monoclonal antibodies specific to the surface glycoproteins (HN and F) of these viruses, as well as to other major virion polypeptides. The long-term objective is to utilize such antibodies for development of improved vaccines and rapid diagnostic tests.

Title of Project: Liposome-Immunostimulant Adjuvant System
Principal Investigator: Kent R. Myers
Awardee Organization: Ribi ImmunoChem Research, Inc.
P.O. Box 1409
Hamilton, MT 59840
Telephone Number: (406) 363-6214
Awardee Number: 1 N43 AI72670-00

This project is directed toward development and testing of a liposomal adjuvant system that will engender a strong and sustained immune response to antigens of low immunogenicity. This adjuvant system will consist of liposomes that contain one or more nontoxic immunopotentiators of microbial or synthetic origin. These immunopotentiators are highly active as adjuvants when administered in oil-in-water emulsions. Two possible modes of antigen incorporation, encapsulation and covalent attachment, will be evaluated. The performance of liposomal adjuvants with polysaccharide, peptide, and protein antigens will be assessed to establish the general utility of this approach.

Several immunological criteria will be used to evaluate these liposomal vaccines: (1) the magnitude of the humoral and cell-mediated immune responses, (2) the distribution of antibody classes and IgG subclasses; and (3) the response to secondary immunizations (immunological memory). The ability of these liposomal vaccines to stimulate nonspecific resistance against an antigenically unrelated pathogen will also be evaluated, using a murine bacterial challenge model.

It is anticipated that data from these experiments will provide a foundation and a rationale for an expanded Phase II project, which will include clinical trials of these liposomal adjuvants in humans.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Phase I Grants

Title of Project: Transforming Growth Factor-βs as Agents for the Treatment of Arthritis
Principal Investigator: Larry R. Ellingsworth, Ph.D.
Awardee Organization: Collagen Corporation
2500 Faber Place
Palo Alto, CA 94303
Telephone Number: (415) 856-0200
Awardee Number: 1 R43 AK38789-01

Two homologous proteins, isolated from demineralized bovine bone and operationally referred to as cartilage-inducing factors-A and -B (CIF-A and CIF-B), have been found to be potent inhibitors of lymphocyte function and to have anti-inflammatory activity. These factors have the same biological activities as the human transforming growth factor-beta (TGF-β). CIF-A and TGF-β appear to be the same molecule (CIF-A/TGF-β), while CIF-B has 63 percent sequence homology.

The following observations suggest these are naturally occurring immunoregulator molecules: (1) These factors are antagonists of interleukin-1 (thymocyte proliferation assay). (2) These factors inhibit mitogen-induced T-cell and B-cell proliferation. (3) These factors are potent inhibitors of IgM and IgG production by plasma cells. (4) These factors are active at <1.0 ng/ml in culture. (5) CIF-A/TGF-β mRNA is detected in mitogen-activated lymphocytes and is secreted by these cells. (6) Exogenous factor down-regulates the interleukin-2 receptor. (7) These factors exhibit anti-inflammatory activity *in vivo*.

In Phase I of this proposal, Collagen Corporation will evaluate the therapeutic use of these factors for the treatment of autoimmune diseases. Polyarthritis will be induced in rats by immunizing with type II collagen. The arthritis will be treated by injecting these immunosuppressive factors into the inflamed joints. The efficacy of treatment will be determined by clinical, immunologic, histopathologic, and radiographic methods. In Phase II, rheumatoid arthritis patients will be treated with therapeutically effective amounts of these factors.

Title of Project: High-Speed DPA Scanner for Diagnosis of Osteoporosis
Principal Investigator: Douglas P. Boyd, Ph.D.
Awardee Organization: Imatron, Inc.
389 Oyster Point Boulevard
South San Francisco, CA 94080
Telephone Number: (415) 583-9964
Awardee Number: 1 R43 AR37189-01

Imatron, Inc. intends to become a major supplier of high-speed dual photon absorptiometry (DPA) scanners to the medical marketplace for aid in the diagnosis and treatment of metabolic bone diseases, such as osteoporosis, which are characterized by changes in bone mass or density. The specific aim of this proposal is to develop and demonstrate an innovative DPA scanner technology that will acquire scans 20 to 50 times faster than conventional technologies, while at the same time doubling or tripling the precision and accuracy of quantitative assessment of bone mineral content in the spine and at other skeletal sites. This goal will be achieved by the development of novel x-ray source and multielement germanium detector concepts to replace the isotope-source, single-detector arrangement of conventional slow-speed DPA scanners.

When developed to commercialization, the Imatron, Inc. high-speed DPA scanner with its high patient throughput capabilities will open up an entirely new realm of applications for DPA

bone measurement, specifically that of mass screening of the general population for early indications of osteoporosis, and will greatly increase the efficacy of interval scanning of patients with acute osteoporosis for disease and treatment monitoring.

Phase II Grants

Title of Project: Topical Prodrugs for Treatment of Acne and Skin Diseases
Principal Investigator: Harlie A. Parish, Ph.D.
Awardee Organization: Molecular Design International, Inc.
P.O. Box 41777
Memphis, TN 38174
Telephone Number: (901) 454-1919
Awardee Number: 2 R44 AR35539-02

The long-term objective of this project is to develop a commercial product(s) for the topical treatment of acne and skin diseases. The specific aim of the proposal is to invent a prodrug that can be used effectively and safely for the topical treatment of acne.

Approximately 60.6 million Americans have skin disorders requiring medical treatment each year. Because isotretinoin (13-cis-retinoic acid, Accutane-Roche) administered orally can cause birth defects and applied topically is irritating, 10 prodrugs of isotretinoin were designed and synthesized in an effort to eliminate these side effects; 9 of these were evaluated during Phase I of the project. Eight of the nine new compounds are as effective as isotretinoin in the topical rhino mouse assay, and seven of these are nonirritating. A U.S. patent was issued in June 1987 and foreign patents are pending.

A topical drug that would retain the effectiveness of isotretinoin but would be free of the deleterious side effects would be technologically innovative and commercially successful. Using quantitative structure-activity relationship (QSAR) predictions from Phase I results, new derivatives have been designed for synthesis and evaluation in Phase II. It is planned to scale up the design and to develop and optimize the lead prodrugs during Phase II. A candidate drug has been identified that is effective and nonirritating.

Title of Project: Ferritin-Linked Immunoassay: A Nonradioactive Method
Principal Investigator: Chia-Ling Hu
Awardee Organization: Standard Scientifics, Inc.
P.O. Box 322
Cambridge, MA 02238
Telephone Number: (617) 449-5125
Awardee Number: 2 R44 AR36791-02

Immunoassay, especially radioimmunoassay (RIA), is the most widely used diagnostic tool in biomedical laboratories. In recent years, its application has spread to such diverse areas as environmental health, veterinary science, agriculture, and the food industry. Concomitant with the expanding market, however, there have been increasing constraints on the use of RIA due to the biological hazards of radioisotopes. Similar to other attempts in seeking an alternative method, Standard Scientifics, Inc. introduced a nonradioactive immunoassay—ferritin-linked immunoassay (FLIA).

During Phase I, it was established that FLIA, in which the antigen is labeled with an iron-containing protein, ferritin, is a candidate to replace RIA. Thus, during Phase II, it is planned to: (1) simplify the procedure by replacing the double-antibody method with a solid-phase method; and (2) upgrade the colorimetric method of iron detection and test an alternative, more sensitive method of iron analysis—the coulometric method. In addition, Standard Scientifics, Inc. plans to develop two biomedically useful prototype FLIA systems for β-human chorionic gonadotropin and prostaglandins. Upon completion of these aims, these research findings will be ready to be developed for commercial production.

Title of Project: An Ultrasound-Based Psoriasis Treatment System
Principal Investigator: Thomas L. Anderson
Awardee Organization: UltraThermics, Inc.
7126 180th Avenue, Northeast
Redmond, WA 98052
Telephone Number: (206) 882-4322
Awardee Number: 2 R44 AR36156-02

Psoriasis is a disease for which new modalities of treatment are needed, especially for chronic, plaque-type lesions with limited skin distribution. Patients and physicians alike are frustrated because none of the existing therapies is completely satisfactory.

Preliminary clinical studies indicate that psoriatic plaques, like cancer tumors, may be cleared as a result of being heated to temperatures in the hyperthermic range (42 to 46°C). Proposed is the development of a relatively simple and inexpensive hyperthermia system capable of treating lesions of psoriasis and other heat-sensitive skin diseases. Under Phase I, a family of low-loss, extremely wide band treatment applicators was developed. A significant feature of the design is that transducers with shapes and sizes well suited for treating those body parts most often affected by psoriasis can be fabricated. Initial patient trials and dosimetry studies indicate that tailored thermal distributions can easily be induced in psoriatic tissues.

Phase II seeks to develop a microprocessor-controlled electronics package capable of dynamically and simultaneously controlling the acoustic frequency and power output of the ultrasound transducer and the temperature of the water cuff that couples the energy to the body, and to enter clinical trials at four research institutions. From these investigations, it is anticipated that optimized treatment protocols will emerge that confirm the safety and efficacy of this new therapy, and thereby create a demand for commercial systems.

NATIONAL CANCER INSTITUTE

Phase I Grants

Title of Project: Immunodirectable MR Contrast Agents
Principal Investigator: Lee Josephson, M.D.
Awardee Organization: Advanced Magnetics, Inc.
61 Mooney Street
Cambridge, MA 02138
Telephone Number: (617) 497-2070
Awardee Number: 1 R43 CA45910-01

A number of syntheses of small magnetic particles permitting the covalent attachment of antibodies will be examined. Changes in magnetic resonance (MR) proton relaxation after magnetic antibodies have bound to cell surface antigens will be utilized to demonstrate the binding of antibody (and magnetic label) to antigens.

The magnetic labels investigated will possess the magnetic properties of a crystal (e.g., high magnetic susceptibility) and the solution properties of soluble macromolecules (e.g., no settling on prolonged standing). One advantage of attaching antibody to magnetic particles, over the often-used approach of derivatizing proteins with chelators, is that far more metal ions can be attached per mole of antibody. In addition, unlike radiolabeled antibodies, magnetic labels show no radioactive decay. Highly magnetic proteins may be useful agents for immunodirectable MR contrast agents.

Title of Project: 3-D Display of Volumetric Data Utilizing Electronic and Holographic Displays with Motion Paraliax
Principal Investigator: Jeffrey Kulick, Ph.D.
Awardee Organization: Aerodyne Products Corporation
76 Treble Cove Road
North Billerica, MA 01862
Telephone Number: (617) 663-7411
Awardee Number: 1 R43 CA42657-01

Medical imaging systems are now producing imagery of such complexity that the traditional slice presentations are insufficient for communicating the information to the observer. Current display techniques, such as producing 2-D projections of 3-D data, are a step in the right direction.

This program is concerned with developing true 3-D display systems that include stereo and motion parallax. Specific techniques being developed include electronic stereo workstations and holographic hard-copy output.

Title of Project: Development of a Controlled-Environment Chamber
Principal Investigator: Gary R. Papas
Awardee Organization: American Boremene, Inc.
53 East Rogues Path
Huntington, NY 11746
Telephone Number: (516) 673-3333
Awardee Number: 1 R43 CA44856-01

The long-term objective is to develop a mechanical device that will provide complete environmental control (temperature, pressure, humidity, sterility, pH, gaseous atmosphere, and light rays) of biological or industrial specimens under microscopic examination. Controls will be maintained even during periods of physical manipulation of the specimen and during microscopic observation through optically clear lenses inherent in the design of the device.

American Boremene, Inc. will work with the Cold Spring Harbor Laboratory to develop this device. The aim is to develop a functional device from a prototype. Specifically, the environmentally controlled chamber will be used for the microinjection of specimens without compromising the integrity of the specimen or the safety of the researcher. The methodology will include a design based on mechanical engineering and physical principles. Existing technology and input from the biomedical sector will be considered. The device will be tested as to its ability to maintain an environment against current laboratory techniques with experiments involving the microinjection of living tissue culture cells.

No technology exists that provides for complete environmental control in an economical format and can be easily managed on the stage of a microscope. Commercial applications that will result from successful research include an increase in the accuracy and efficiency of experiments requiring environmental control, a means of protecting researchers from hostile organisms or noxious materials, an improvement in the success rate of human *in vitro* fertilization, and an energy cost reduction during petroleum distillation.

Title of Project: Distributed Data Management for Cancer Clinical Trials
Principal Investigator: Jamie C. Bayer, Ph.D.
Awardee Organization: Analytic Methods, Inc.
8409 Southwest 3rd Place
Gainesville, FL 32607
Telephone Number: (904) 371-1086
Awardee Number: 1 R43 CA43376-01

This proposal seeks to develop and implement a distributed data management network for cancer clinical trials. The network will be microcomputer based and will have as its objective a centralized database for monitoring the progress of clinical trials. Features will include data entry using preformatted screens, automated error checking, editing facilities, data security, and data transfer capability between compatible machines. The network will use existing, commercially available database software as a vehicle, with customized applications for patient registration, data submission, quality assurance notification, study coordinator review, database updates, information exchange with treating institutions, statistical tabulations, and report preparation.

Title of Project: New Target-Directed Pt-Porphyrin Anticancer Drugs
Principal Investigator: Paul Schwartz, Ph.D.
Awardee Organization: Andrulis Research Corporation
7315 Wisconsin Avenue, Suite 650N
Bethesda, MD 20814
Telephone Number: (301) 657-1700
Awardee Number: 1 R43 CA44229-01

The objective of this project is to improve the selectivity of action of platinum antitumor agents. Platinum compounds have shown activity in many types of tumors, but severe dose-limiting side effects have affected their clinical utility. By directing these agents more specifically to tumor sites, their effectiveness should be improved. The approach used to achieve this improved specificity will be to link them to synthetic porphyrins that are known to have tumor-localizing properties.

Platinum complexes having known antitumor activity will be chemically reacted with substituted tetraphenylporphyrin compounds. The reaction conditions will assure stable binding of the active Pt moiety to the substituent sites on the porphyrin ring rather than at the central site. In this way, the porphyrin that accumulates in tumor tissue can act as a carrier to the tumor for the active Pt species.

The success of this program will lead to new, more specific antitumor agents, a major goal in the design of new drugs.

Title of Project: A Methioninase for Methionine-Dependent Chemotherapy
Principal Investigator: Peter H. Stern, Ph.D.
Awardee Organization: AntiCancer, Inc.
P.O. Box 296
La Jolla, CA 92038
Telephone Number: (619) 299-3250
Awardee Number: 1 R43 CA43444-01A2

New approaches are necessary to improve chemotherapy of solid tumors. For this purpose, AntiCancer, Inc. has taken advantage of the cancer-specific metabolic defect of methionine dependence, which causes many types of cancer cells to reversibly arrest late in the S/G_2 phase of the cell cycle in medium where methionine (Met) has been replaced by homocysteine (Hcy) (Met^-Hcy^+ medium). This approach has been termed "methionine-dependent chemotherapy."

To bring methionine-dependent chemotherapy closer to clinical trials, AntiCancer, Inc. proposes to isolate a methioninase that, upon administration to the animal or patient, will allow the modulation of circulating levels of methionine. The bacteria *Alcaligenes faecalis* and *Pseudomonas pseudoalcaligenes*, which contain a methioninase that apparently does not cleave homocysteine, have been identified. State-of-the-art genetic selection and protein purification procedures will be used to isolate a methioninase with a low K_m, a long half-life in the circulation, and a low toxicity for the experimental animal or human patient. The methionine-cleaving properties, half-life, and toxicity of the enzyme will be tested in rats. Purification and characterization of a desirable enzyme in Phase I will lead to cloning the methioninase gene in Phase II.

Title of Project: New Photon Detector for Positron Emission Tomography
Principal Investigator: A.K. Drukier, Ph.D.
Awardee Organization: Applied Research Corporation
8201 Corporate Drive, Suite 920
Landover, MD 20785
Telephone Number: (301) 459-8833
Awardee Number: 1 R43 CA45986-01

Applied Research Corporation proposes to develop a novel type of particle/photon detector based on energy-sensitive superconducting structures. In positron emission tomography (PET) and single-photon emission-computerized tomography (SPECT) applications, it promises substantial improvements in image quality due to sub-millimetric spatial resolution, very fast, subnanosecond read-out, and very high-stopping power for high-energy photons.

The development of a new ring detector that features both SPECT and PET imaging capabilities is suggested.

Title of Project: A New Position-Sensitive X-Ray Detector
Principal Investigator: A.K. Drukier, Ph.D.
Awardee Organization: Applied Research Corporation
8201 Corporate Drive, Suite 920
Landover, MD 20785
Telephone Number: (301) 459-8833
Awardee Number: 1 R43 CA45989-01

Applied Research Corporation (ARC) proposes to develop a new class of solid-state particle/radiation detectors. Arrays of these detectors will provide images with superior quality. More specifically, ARC proposes to develop soft x-ray detectors (E=0.5 to 20 keV) for biological applications, e.g., protein crystallography. The proposed detector will advance present material characterization capabilities by improving spatial, angular, and energy resolution. Furthermore, it is radiation hard and permits imaging of very high fluxes, over 1 million photons per second, in both UV and soft x-rays. Subsequently, a 2,048 × 2,048 pixel array with count rates better than 10^8 counts per second will be developed for applications in synchrotron radiation and free-electron laser facilities.

The detector is based on energy-sensitive superconducting structures and has been tested with x-ray sources. In Phase I, ARC will perform a series of measurements of quantum detection efficiency (QDE). Detector properties (energy resolution, stopping power) for application as a high-spatial-resolution detector will be optimized. Read-out electronics for a small array detector, e.g., 64 × 64 pixels, will also be developed and tested.

Title of Project: Cell Panels for Testing Monoclonal Antibodies
Principal Investigator: Allyn H. Rule, Ph.D.
Awardee Organization: ASA Rule, Inc.
225 Crescent Street
Waltham, MA 02154
Telephone Number: (617) 647-5598
Awardee Number: 1 R43 CA45880-01

Optimal evaluation of monoclonal antibodies (Mab) frequently requires use of quick-frozen cells or tissues not readily available to research and commercial groups. ASA Rule, Inc. plans to develop a rapid service to screen Mabs. This will require the availability of well-organized, quick-frozen panels of normal, benign, and malignant cells (disaggregates or tissues) frozen and maintained at −80°C for rapid screening. When feasible, these cell samples will be covalently linked to glass.

Methodologies will be developed (1) for cell meshing, mincing, and dispersal from solid tissues or tumors; (2) for tissue preparation by enzyme treatment with collagenase, trypsin, papain DNA-ase dispase and/or neuraminidase, compared to no treatment of tissue slices; and (3) for separation of cells from debris using density gradients prior to adhesion to activated wells and quick freezing. Methods will be specifically devised and optimized for each organ/tumor system. The immediate aim is to develop the technologies needed to disperse cells prior to freezing. The long-term aim is to develop a service for the assessment of monoclonal antibodies using quick-frozen, viable, cell panels maintained at −80°C.

Title of Project: Development of a Clinician's Information System
Principal Investigator: Daniel Kerner, Ph.D.
Awardee Organization: Civilized Software, Inc.
7735 Old Georgetown Road, Suite 410
Bethesda, MD 20814
Telephone Number: (301) 652-4714
Awardee Number: 1 R43 CA44076-01A1

The research proposed is to investigate the feasibility of writing a software package for personal workstations that will help clinical researchers and their assistants carry out the design, data collection, data storage, and formal and exploratory analyses of clinical trials. The purpose of such software will be to assist the single researcher or the small group doing small- to moderate-sized trials.

Tools will be developed that are easy to use and time efficient; they will provide a framework similar to (but more powerful than) the paper-based systems researchers typically use. The tools will emphasize acquiring the highest quality data via data management methods specific for the clinical investigator, and using various graphical and exploratory analysis methods that substitute computer-intensive techniques for classical techniques requiring more assumptions. Tools will also be included to design (or evaluate the design of) clinical trials using clinically understandable parameters, such as percentages or hypothetical curves as input, with regard to sample size and statistical power.

Title of Project: Automated Synthesis of Nitrogen-13-Labeled Octylamine
Principal Investigator: Maria Straatmann
Awardee Organization: Computer Technology and Imaging, Inc.
215 Center Park Drive
Knoxville, TN 37922
Telephone Number: (615) 966-7539
Awardee Number: 1 R43 CA44491-01

The development of an automated synthesis module (ASM) for the production of nitrogen-13-labeled octylamine is proposed. Nitrogen-13-labeled octylamine is a promising lung-imaging agent. However, because of the short half-life of nitrogen-13 (10 minutes), the synthesis must be performed in a rapid, automated module for widespread utilization in the hospital environment. The new ASM module will efficiently remove the nitrogen isotope from the target of the small medical cyclotron and perform the necessary chemistry to produce the desired nitrogen-

13-labeled octylamine within 30 minutes.

The commercial availability of such an effective lung-imaging agent, combined with the many other innovations presently occurring in positron emission tomography (PET), could greatly enhance PET. Computer Technology and Imaging, Inc. is developing and will begin supplying PET centers with systems that will sell for less than typical magnetic resonance imaging scanners.

Title of Project: Movement-Detection System for PET Scanners
Principal Investigator: Ronald Nutt, Ph.D.
Awardee Organization: Computer Technology and Imaging, Inc.
810 Innovation Drive
Knoxville, TN 37932
Telephone Number: (615) 966-7539
Awardee Number: 1 R43 CA45854-01

During a positron emission tomography (PET) scan, movement by the subject of more than 1 mm will cause noticeable blurring of the image. Movement will also cause artifacts to be introduced into the image because the matrix for correcting for gamma-ray absorption is determined for a specific position.

This proposal outlines the development of a movement-detection system using a small array of ultrasonic transducers that train narrow beams of ultrasound on selected areas on the subject in the image volume. Movement of the subject from the initial position will be detected by measuring the change in transit time of the sound reflected back to the transducers. If motion exceeding the preset acceptable amount occurs, the system will automatically stop data acquisition and display the displacements for each transducer, so that the operator can move the subject back into position before resuming data acquisition. This movement-detection system will allow more efficient use of the expensive PET systems, insure better imaging, and help eliminate repeat injection of the subject with radioactive isotopes.

Title of Project: Computer Software for Hyperthermia Treatments
Principal Investigator: Arkady S. Dvinsky, Ph.D.
Awardee Organization: Creare, Inc.
P.O. Box 71, Etna Road
Hanover, NH 03755
Telephone Number: (603) 643-3800
Awardee Number: 1 R43 CA45117-01

Strong evidence exists that elevated temperatures, in the range of 42 to 45°C (hyperthermia), are an important factor in the destruction of cancer cells, especially when combined with radiation therapy and chemotherapy. Producing a controlled-temperature distribution of a given magnitude is critical to the success of hyperthermia treatment. Recent advances in computer technology have made numerical modeling of hyperthermia treatment a viable alternative for predicting the temperature distribution in tissue.

Creare, Inc. proposes to develop and test a three-dimensional computer model for quantitative thermal dosimetry to be used in hyperthermia treatments. Based on the specified anatomy of the patient and the characteristics of the heating device, a computer program will predict power deposition and temperature fields in the tissue. The calculated results will be displayed interactively in graphic and alphanumeric form. The developed software will be a powerful tool for patient treatment planning, design and testing of equipment, posttreatment evaluation, and scientific research.

In Phase I, specifications for the computer model of hyperthermia treatment will be developed. In addition, a computer program for calculating power deposition in realistic two-dimensional geometries will be implemented.

Title of Project: Software for Longitudinal Data Analysis Related to Cancer Etiology
Principal Investigator: Cyrus R. Mehta, Ph.D.
Awardee Organization: Cytel Software Corporation
137 Erie Street
Cambridge, MA 02139
Telephone Number: (617) 661-2011
Awardee Number: 1 R43 CA45901-01

Longitudinal studies play an increasingly prominent role in biomedical research. Examples from the cancer field include analysis of repeated tumor marker measurements, tumor growth curve analysis for animal bioassay, and changes in body weight for patients on cancer clinical trials. In the past, analysis of such data was based on strong, but unverifiable, parametric assumptions about the data-generating process. Recently, there have been several important methodological advances that enable longitudinal data to be analyzed by nonparametric and semi-nonparametric methods. Moreover, these methods remain valid in the presence of missing data and time-varying covariates.

The main goals of this Phase I proposal are (1) to unify these methodologic advances by providing a single, semi-nonparametric (quasi-likelihood) approach that can be used with either continuous or categorical repeated measures data, with possibly missing observations, and possibly time-varying covariates; (2) to demonstrate the feasibility of developing statistical software, meeting commercial standards of friendliness and reliability, to implement the new analytical techniques; and (3) to analyze some real longitudinal data sets with newly developed demonstration software. The experience gained in this Phase I endeavor will be used during Phase II to develop a comprehensive, commercially viable statistical package for longitudinal data analysis on mainframe, mini-, and microcomputers.

Title of Project: Ultrasound Doppler/B-Mode Breast Scanner
Principal Investigator: Peder C. Pedersen, Ph.D.
Awardee Organization: Daltex Medical Sciences, Inc.
20 Exchange Place
New York, NY 10005
Telephone Number: (212) 514-6255
Awardee Number: 1 R43 CA44201-01

The proposed research is intended to show the feasibility of developing a commercial ultrasound mammography system (nonionizing modality) with a detection ability similar to X-ray mammography systems (lesions 5 mm or less), and based on combined tissue and blood-flow imaging. The blood-flow imaging is significant, since malignant tumors exhibit dramatically increased vascularity and blood flow when measured with ultrasound Doppler. The instrument is intended for both screening and diagnosis.

To overcome the limitations of conventional ultrasound mammography, several new imaging concepts will be evaluated. The received pulse-echo ultrasound RF data of a full image will be digitized to greatly increase the flexibility of the software processing. The digital signal processing will produce both a tissue-structure image and a blood-flow image of the scanning plane. The negative pressure sensitivity of tumor blood flow will be investigated separately as a possible method of differentiating between benign and malignant lesions by use of a special scanning tank. This scanning tank design will also permit its use with the patient in a sitting or standing position. For evaluation of the mammography system, ultrasound scanning of normal volunteers and women with diagnosed breast cancer is planned.

Title of Project: A Real-Time, High-Resolution (1023 Line/16MHz) Analog Video Recorde.
Principal Investigator: Vincent D. Kasprzak
Awardee Organization: Delta Research Group, Inc.
1080 Linda Vista Avenue
Mountain View, CA 94043
Telephone Number: (415) 961-4300
Awardee Number: 1 R43 CA45103-01

The absence of real-time recording subsystems with resolution to match medical imaging modalities severely limits diagnostic capabilities and unnecessarily extends patient procedures, hazards, and costs.

Research staff are in place with a fully equipped recording laboratory. Phase I will involve applied research for a 16-MHz analog magnetic tape recorder using frequency multiplexing for recording images at 1,023 lines, while maintaining equal resolution along both vertical and horizontal axes. This recording capability is not commercially available in any product today.

The Phase I objectives are system architecture, block diagrams, critical multiplexing component testing of double-balanced mixers, filters, and video OP AMPs. This project capitalizes on transport components of proven merit currently in high-volume manufacture; this permits development to focus on multiplexing technologies. The primary result lies in proofing system specifications of (1) bandwidth; (2) signal-to-noise ratio; and (3) time base stability.

Phase II objectives will be determined by these results. This product will allow interfacing with major medical research institutions, recording industry technical committees, U.S. and offshore technology sources, and dominant medical OEMs.

Title of Project: A Real-Time Multifunction Video Format Converter
Principal Investigator: Vincent D. Kasprzak
Awardee Organization: Delta Research Group, Inc.
1080 Linda Vista Avenue
Mountain View, CA 94043
Telephone Number: (415) 961-4300
Awardee Number: 1 R43 CA44220-01

The absence of a multifunction format converter to convert 525-line/5-MHz video to ,023-line rate display, progressive or interlaced, results in excessive costs by overspecification of video chains without corresponding diagnostic values.

Phase I will involve applied research on real-time pixel interpolation techniques (up-converting line rates) to enable 1,023-line display for line structure filtering of 525-line/5-MHz video, progressive or interlaced (scan conversion), with systems provisions for multiframe stores.

Phase I objectives are to investigate system architecture, critical circuits, components, and sources; establish preliminary designs and construct breadboards; and conduct medical-site evaluations of diagnostic merit at the Mayo Clinic.

These innovative functions will obviate the trend to high-resolution video chains by enabling display of 525-line/5-MHz progressive video on 1,023-line interlace monitors. This curtails the cost or need for replacement of all other 525-line/5-MHz video chain components, while significantly improving diagnostic usefulness.

Title of Project: Dereplication of Antitumor/Cytotoxic Natural Products
Principal Investigator: James C. French, Ph.D.
Awardee Organization: DEREP, Inc.
3150 Rumsey
Ann Arbor, MI 48105
Telephone Number: (313) 665-7171
Awardee Number: 1 R43 CA45087-01

The elimination (dereplication) of known natural products and duplicate leads from screening programs as early as possible is of utmost importance to assure that maximum attention is given to truly novel compounds. The development of a computerized databank is proposed. It will contain information for the rapid exclusion of known, biologically active compounds encountered during the screening of microorganisms, fungi, higher plants, and marine organisms.

Emphasis will be placed upon ultraviolet absorption and molecular weight information. These data are usually the first definitive properties detected in semipurified concentrates of natural products obtained during the very early stages of isolation work. Several other data fields such as structure type, molecular formula, related compounds, producing organism, and elemental analysis are included. Key literature references to each compound are cited so that detailed information about compounds retrieved from searches of the database can be readily obtained.

This database will be programmed so that it can be easily searched, using search criteria that are most important for the dereplication of unknown natural products. Also, a convenient procedure will be provided to obtain summary or full reports of related compounds having, for example, the same structure types, activities, and/or molecular weights or molecular formulas within a specified range.

Title of Project: Image Telecommunication for Radiation Therapy Planning
Principal Investigator: Hirsch Handmaker, Ph.D.
Awardee Organization: Diagnostic Networks, Inc.
1361 Bush Street
San Francisco, CA 94109
Telephone Number: (415) 474-3711
Awardee Number: 1 R43 CA42646-01

Optimal radiation therapy for cancer in most instances requires multislice computer tomography (CT) or magnetic resonance (MR) studies of the cancer and adjacent structures for the preparation of sophisticated, computerized, three-dimensional treatment plans. The cost of these technologically advanced computers and software to perform state-of-the-art radiation therapy treatment planning is high. For many radiation therapy departments the cost is too great to permit access to the current technology.

The aim of this project is to develop a low-cost, relatively high-speed image telecommunication system that will make it feasible for radiation therapy departments to transmit CT and/or MR images to a centralized regional radiation therapy treatment planning center for the computerized preparation of treatment plans.

A telecommunication system based on microcomputer processors with local hard-disk storage, high resolution (1,024 × 1,024 × 12 bit monitors), and 9,600 baud modems is proposed. The study seeks to test telecommunication and processing speed, and the accuracy of data transmission.

Title of Project: Initiation-Promotion Bioassay in Mouse Liver
Principal Investigator: Michael A. Pereira
Awardee Organization: Environmental Health Research and Testing, Inc.
3235 Omni Drive
Cincinnati, OH 45245
Telephone Number: (513) 752-2950
Awardee Number: 1 R43 CA45110-01

Short-term/limited bioassays for the detection of chemical carcinogens, tumor initiators, and tumor promoters have been recognized as important components to the determination of the carcinogenic hazard of environmental chemicals and complex mixtures. These bioassays are useful to determine (1) whether a substance is carcinogenic, (2) dose-response relationships, and (3) mechanism, i.e., tumor initiator and/or promoter. Many of the chemicals that have been positive in the long-term carcinogenesis bioassay were active in mouse liver.

The proposed objectives of this project are to determine whether the 15-day-old mouse liver initiation-promotion bioassay can be used to distinguish carcinogens from noncarcinogens and then to develop the bioassay so that it can be used to determine their mechanism of action. C3H and B6C3F1 male mice will be used because (1) studies determined them to be sensitive strains and sex, (2) the B6C3F1 mouse is used in the NTP long-term bioassay, and (3) opposing effects of phenobarbitol on diethylnitrosamine (DENA)-initiated hepatocarcinogenesis have been found (promotion in B6C3F1 and inhibition in C3H).

In Phase I, the relative sensitivity of the two strains of mice to different chemical classes and the effect of phenobarbitol will be determined. The protocol will consist of (1) administering the test substance to male mice on day 15 of age, (2) starting at weaning and continuing until sacrifice, administering 500 ppm sodium phenobarbitol in the drinking water, (3) sacrificing the mice at 180 days of age, and (4) evaluating the liver for neoplastic lesions. Once the protocol for the 15-day-old mouse initiation-promotion bioassay has been developed, Phase II will evaluate the ability of the assay to determine dose-response and structure-activity relationships, and to distinguish tumor initiators and promoters.

Title of Project: Amino Acid-Degrading Enzymes as Anticancer Agents
Principal Investigator: Frank F. Davis, Ph.D.
Awardee Organization: Enzon, Inc.
300-C Corporate Court
South Plainfield, NJ 07080
Telephone Number: (201) 668-1800
Awardee Number: 1 R43 CA45897-01

Enzon, Inc. is involved in the development of therapeutic enzymes for human and veterinary use. Many enzymes have shown effectiveness as anticancer agents on initial injection, but their immunogenicity and short plasma half-life have prevented exploitation of their potential. Enzon, Inc. will modify two glutaminase-asparaginases and a histidase using a patented company process to produce enzyme-polyethylene glycol (PEG) conjugates with vastly improved plasma half-lives and greatly reduced immunogenicities. These PEG enzymes can be injected repeatedly so that their full therapeutic potential can be realized. Enzon, Inc. will perform plasma half-life and initial toxicological studies on the three PEG enzymes.

The long-term objective is to obtain Investigational New Drug (IND) approval and commence clinical studies. These enzymes are the forerunners of a larger group of nonessential and essential amino acid-degrading enzymes that will be developed as therapeutic agents for various types of cancer.

Title of Project: CCD Detector Development for Digital X-Ray Mammography
Principal Investigator: David E. Gustafson, Ph.D.
Awardee Organization: Fischer Imaging Corporation
12300 North Grant Street
Denver, CO 80241
Telephone Number: (303) 452-6800
Awardee Number: 1 R43 CA45856-01

A high-resolution scanned-projection radiography system is proposed for digital mammographic applications. By using a wide, dynamic-range CCD detector, some of the current limitations encountered in conventional film-screen mammography can be avoided. One-dimensional, fan-beam geometry provides very good scattered x-ray reduction. A time-delay-and-integrate (TDI) mode of CCD imaging with a 2,048 × 96 element CCD array provides the opportunity to image without the excessive power-loading of x-ray tubes that would be required with a 2,048 × 1 array. By utilizing TDI charge integration while the detector is scanned, each projection through stationary anatomy is averaged over 96 exposures, thereby providing a significant signal-to-quantum mottle improvement of approximately 10:1 when compared to a 2,048 × 1 detector at the equivalent tube loading.

Developmental tasks to be performed include construction of a TDI-CCD x-ray detector in which the light output of an x-ray-intensifying screen is coupled by means of a lens to the CCD focal plane, measurement of x-ray sensitivity, assessment of noise characteristics and homogeneity of the x-ray detector construction of a moving-sample x-ray imaging system based on the TDI detector, and determination of the optimum x-ray spectrum for digital mammographic imaging tasks to evaluate its clinical potential.

Title of Project: Continuous Flow System for Hybridoma Microencapsulation
Principal Investigator: Harris Gold, Ph.D.
Awardee Organization: Foster-Miller, Inc.
350 Second Avenue
Waltham, MA 02254
Telephone Number: (617) 890-3200
Awardee Number: 1 R43 CA41913-01A1

The aim of this Phase I research is to develop laboratory data on and a theoretical model of an innovative concept of a continuous flow system for the gelation of alginate microencapsulated hybridoma cells and the transfer of the resulting gelled alginate spheres from a toxic calcium environment to a saline environment. The primary purpose of the experiments is to see if it is possible to control the capsule residence time and produce uniformly reproducible capsules. A secondary purpose is to enhance the volume of monoclonal antibody production over that now achievable by batch procedures and minimize serum usage.

A laboratory-scale, nonsterile, Plexiglas free-fall and packed bed-wash column will be set up for measurement of the physical-chemical parameters. The alginate drops from a drop former on top of the free-fall column will be gelled into capsules upon falling into a calcium chloride solution. The capsules will be continuously transferred to a moving bed-wash column where the calcium solution will be replaced by a saline solution. The parameter range for continuous and stable operation will be measured. Simultaneously, a theoretical modeling analysis will be undertaken. Employing the laboratory data and theoretical results, generic relations will be set out to define optimal operation and scaling laws in terms of the system parameters.

National Institutes of Health
National Cancer Institute

Title of Project: L5178Y Mouse Lymphoma TK Locus Host-Mediated Assay
Principal Investigator: Ann D. Mitchell, Ph.D.
Awardee Organization: Genesys Research, Inc.
2520 Wyandotte Street
Mountain View, CA 94043
Telephone Number: (415) 968-3635
Awardee Number: 1 R43 CA45903-01

Phase I research will be directed toward developing a new host-mediated assay in which L5178Y mouse lymphoma cells, heterozygous at the thymidine kinase locus and in diffusion chambers in mice, will be exposed to the *in vivo* metabolic activation and detoxification of chemicals. Induction of mutagenesis will be measured *in vitro*. The results of testing selected chemicals in the mouse lymphoma host-mediated assay (MLHMA) will be compared with the results of testing the same chemicals in the *in vitro* mouse lymphoma cell mutagenesis assay (MLA).

It is anticipated that the MLHMA will yield greater concordance of results with *in vivo* carcinogenesis bioassays than does the MLA, and that the MLHMA will fill a current urgent need for an efficient and economical genetic toxicology assay to measure mutagenesis in mammalian cells following *in vivo* exposures to chemicals that may be potentially hazardous to humans. If Phase I research is successful, long-term Phase II research will be proposed to develop multiple-endpoint *in vivo* assays that incorporate the MLHMA and to evaluate a larger number of chemicals from diverse classes.

Title of Project: A Simultaneous Multivial Beta Counter
Principal Investigator: Ralph S. Conti, Ph.D.
Awardee Organization: Hines Industries, Inc.
661 Airport Boulevard
Ann Arbor, MI 48104
Telephone Number: (313) 769-2200
Awardee Number: 1 R43 CA44223-01

A novel principle for simultaneous scintillation counting of multiple radioactive samples is proposed. The immediate goal of this proposal is to construct and test a six-sample prototype device to prove the practical applicability of the principle involved.

The long-term goal is to develop a device that can measure simultaneously the radioactivity in more than 100 liquid scintillation samples. Such a device would lower the cost per minute of counting radioactive samples. Consequently, more samples can be measured for the same cost and lower levels of radioactivity can be used, reducing sample size and the amount of radioactivity required. This will decrease the hazard to laboratory personnel, reduce environmental pollution, and lower the cost of disposal. This innovation has application to all sectors of biomedical research.

Title of Project: *Polyporus umbellatus*: A New Biological Response Modifier
Principal Investigator: J. Peter Fuhrer, Ph.D.
Awardee Organization: Hipple Cancer Research Corporation
4100 South Kettering Boulevard
Dayton, OH 45439-2092
Telephone Number: (513) 299-7120
Awardee Number: 1 R43 CA45885-01

The pharmacological activities of an extract of *Polyporus umbellatus*, a mushroom indigenous to China, have been investigated extensively by the State Pharmaceutical Administration of China. Compound 757, a polysaccharide purified from the extract, has been shown to have antitumor and immunomodulatory activities and already is in clinical trials within China. It has never been used outside of China to date. The Hipple Cancer Research Corporation has obtained sufficient amounts of this new and potentially useful antineoplastic agent. It will be evaluated for its tumoricidal effects, for its clinical toxicities, and for its potential as a commercial product.

In Phase I of this project, compound 757 will be evaluated to determine its direct effect on a broad spectrum of human tumors with the *in vitro* clonogenic assay. The potential toxic effects of the compound will be determined *in vitro* on cells of the hematopoietic system. The possible immunomodulatory effect of the compound will be assessed, and the cytoprotective effect of the compound on normal bone marrow in the presence of antineoplastic drugs will also be determined. Finally, the feasibility of utilizing compound 757 as a chemotherapeutic agent will be brought in a technology-transfer fashion to the pharmaceutical industry for development.

Title of Project: Optimizing Multiparameter Flow Cytometry of Tumor Cells
Principal Investigator: Howard M. Shapiro, M.D.
Awardee Organization: Howard M. Shapiro, M.D., P.C.
283 Highland Avenue
West Newton, MA 02165
Telephone Number: (617) 965-6044
Awardee Number: 1 R43 CA44190-01

Flow cytometry of such parameters as DNA, RNA, surface and/or internal antigen, and total protein content of tumor cells or nuclei is widely used in cancer research and is finding increasing clinical application. Useful information about the biology of normal and abnormal cellular development, the perturbation of cell function by therapeutic agents, and the biologic behavior of tumors in patients, obtained from one- and two-parameter flow cytometry, has led investigators to attempt more sophisticated studies in which DNA, RNA, one or more cellular antigens, and light scattering or extinction are measured simultaneously. The multiple-beam apparatus and many of the staining procedures usable for such analyses have been developed; however, the techniques have remained inaccessible to many investigators because of the difficulty and cost of implementing them on conventional commercial flow cytometers. The present study will examine the performance of two newer flow cytometers using low-power laser light sources in multiparameter analysis of DNA, RNA, and immunofluorescence and/or protein content in cells derived from human tumors. These instruments, potentially much more affordable and easier to use than existing systems, could make it possible for many more laboratories to pursue clinical and experimental applications of multiparameter flow cytometry.

Title of Project: Azaanthracenediones as Antitumor Agents
Principal Investigator: Donald H. Browning, Ph.D.
Awardee Organization: Humphrey Chemical Company
P.O. Box 325
North Haven, CT 06473
Telephone Number: (203) 281-0012
Awardee Number: 1 R43 CA45101-01

The objective of this proposal is an integration of a chemical and biological approach to the commercial development of a new heterocyclic antitumor agent. Humphrey Chemical Company proposes to synthesize and biologically evaluate a series of azaanthracene-9,10-diones. The goal is the commercialization of an antitumor agent that lacks the inherent cardiotoxicity currently exhibited by antineoplastic agents such as mitoxantrone.

Title of Project: Assay of Nucleosides in Small-Cell Carcinoma of the Lung
Principal Investigator: John E. McEntire, Ph.D.
Awardee Organization: IMBIC Corporation
P.O. Box 7539
Columbia, MO 65205
Telephone Number: (314) 874-2481
Awardee Number: 1 R43 CA45844-01

Several investigators have implicated modified ribonucleosides, presumably modification products from transfer ribonucleic acids (tRNAs), as potential biological markers for cancer. Elevated levels of these molecules have been quantitated in the serum or urine of cancer patients by high-performance liquid chromatography-ultraviolet (HPLC-UV) or immunoassay.

In this proposal, IMBIC Corporation will demonstrate the feasibility of preparing antibodies to two common modified nucleosides and the development of an immunoassay for their easy quantitation. Additionally, the levels of 30 modified nucleosides will be determined in the serum from lung cancer patients and normal controls. These data will be subjected to pattern recognition analysis to develop a profile of selected serum-modified nucleoside concentrations that can define biological markers for lung cancer. An immunoassay diagnostic kit will be developed to detect these biomarkers with high sensitivity and specificity.

Title of Project: A Tool to Modify Physician Use of Diagnostic Imaging
Principal Investigator: Barry P. Chaiken
Awardee Organization: Infomedics, Inc.
304 Otis Street
West Newton, MA 02165
Telephone Number: (617) 965-0536
Awardee Number: 1 R43 CA45863-01

One source of escalating American health care costs is physician use of unnecessary diagnostic x-rays. Infomedics, Inc. has developed a set of computer-driven algorithms that can prescreen physician orders for diagnostic imaging procedures and provide feedback to the physician about the predicted information value of each order, thus allowing the opportunity to forego nonproductive procedures. The result will be a decrease in health care costs without compromising the quality of patient care.

The goal of this proposal is to pursue two related objectives: evaluation of the concept of prescreening of imaging procedure requests and evaluation/refinement of the actual product. The first objective will be achieved by interviewing personnel in a variety of hospitals, focus groups, and potential users of the system. The second objective will be achieved by installing the system in a local hospital emergency room and assessing its acceptability, impact on physician attitudes and knowledge, impact on physician ordering patterns, and impact on hospital costs.

If the project is successful, it will provide the opportunity for hospitals to control one segment of institutional costs by the focused application of a clinically relevant educational tool.

Title of Project: Toxic Peptides as Immunotoxin Components
Principal Investigator: Mark B. Chandler, Ph.D.
Awardee Organization: Inland Laboratories
10125 Metropolitan Drive
Austin, TX 78758
Telephone Number: (512) 834-1838
Awardee Number: 1 R43 CA44200-01

Immunotoxins combine the activity of a powerful toxin with an antibody capable of delivering the conjugate to a specific target cell. These compounds have proven effective in the *in vitro* elimination of a number of cell types, including leukemia cells and the bone marrow cells implicated in graft versus host disease. Immunotoxins may thus be an effective way of controlling a number of diseases attributable to a population of antigenically distinct cells.

The *in vivo* use of immunotoxins is currently limited by an unacceptably high level of nonspecific toxicity. This is likely to result from the ability of the toxic component to enter the cytosol without antibody help. The goal of this research is to develop immunotoxin components that retain their intracellular toxicity, but are incapable of transmembrane relocation unless bound to antibody.

Five ribosome-inactivating proteins capable of functioning as immunotoxin components will be enzymatically or chemically cleaved into smaller peptides. It is hoped that by this process functional domains of the toxins can be found that retain the ability to catalytically inactivate ribosomes, but are incapable of self-directed entry into the cytosol. The activity of these peptides will be tested *in vitro* in whole-cell and cell-free assays of protein synthesis, as well as *in vivo* where the LD_{50} of active peptides will be compared to that of the intact toxin. The amino acid sequence of active peptides will also be determined.

Title of Project: Identifying Facilitators and Inhibitors of Breast Screening
Principal Investigator: Steven D. Jones, Ph.D.
Awardee Organization: Institute for Organizational Behavior Research
5320 Calhoun Road
Houston, TX 77021
Telephone Number: (713) 749-7145
Awardee Number: 1 R43 CA44184-01

Although regular breast screenings in the form of mammograms and physical breast examinations are important for the control of breast cancer, only a small percentage of women are receiving such screenings. This project deals with ways to increase the number of women who have such breast screenings.

This project has three long-range objectives: (1) to identify the strength of all the factors that operate as facilitators and inhibitors of the decision to have breast screenings done; (2) to develop and evaluate a methodology for predicting the effectiveness of different strategies that could be used to increase the number of women who have screenings done; and (3) to identify and assess the success of different marketing/outreach strategies that have been used in the past by breast clinics.

Phase I objectives are to comprehensively identify the factors that serve as facilitators and inhibitors to the decision to have screenings done and to begin the process of identifying the marketing/outreach strategies that breast clinics have used in the past.

Title of Project: Dose Distribution Measurements with Thin TLD Arrays
Principal Investigator: P.F. Braunlich, Ph.D.
Awardee Organization: International Sensor Technology, Inc.
Southwest 790 City View
Pullman, WA 99163
Telephone Number: (509) 332-3328
Awardee Number: 1 R43 CA44242-01

International Sensor Technology, Inc. (IST) proposes to develop a thermoluminescence dosimetry (TLD) system for measurement of absorbed dose distributions of ionizing radiation (gammas, betas, neutrons) in phantoms. The system will employ IST-developed technology for laser heating and fabrication of suitable large-area, thin-film dosimeter arrays. Commercial thermoluminescence (TL) phosphors (e.g., magnesium borate) will be used with a printing technique for producing various spot sizes and thicknesses on thin glass or high-temperature polymer-substrate sheets. Neutron doses can be measured using proton radiators and proton absorbers on alternate spots, or using a TL phosphor made with different isotopes at alternate locations, for gamma-neutron discrimination.

The TLD system will be based on a highly stable, closed-loop, feedback-controlled 20-watt CO_2 laser with a beam that has a uniform cross section of variable size. The temporal shape of the laser heating pulse will be tailored by computer control for pre- and postanneal treatments and rapid heating of these dosimeters with minimal incandescence background emission. A large reading area will be obtained by the addition of special X-Y dosimeter-positioning mechanisms.

The advantage of the proposed technology over conventional phantom dosimetry is the possibility of placing a large number of very small dosimeters in the form of arrays on sheets between the transverse slices of human phantoms or wrapping them around bonelike or prosthetic material inserted in these phantoms and rapidly measuring the absorbed doses in an automated TLD reader.

Title of Project: Use of Adaptive Beam Forming in Clinical Ultrasound
Principal Investigator: Kai E. Thomenius
Awardee Organization: Interspec, Inc.
1100 East Hector Street
Conshohocken, PA 19428
Telephone Number: (215) 834-1511
Awardee Number: 1 R43 CA45871-01

The overall goal of the project is to improve resolution when using large-aperture, phased linear arrays in clinical ultrasound. In particular, means will be developed to eliminate beam-forming errors caused by variations of sound velocity in the organs being imaged or by phase errors in the system hardware itself. It is believed that current clinical instruments fail to achieve their potential resolution due to these sound speed variations. This research will evaluate the feasibility of adaptive beam-forming techniques to correct for the resulting phase errors. Algorithms derived from adaptive optics will be modified for use in medical ultrasound.

Application of a successful algorithm to commercial instruments during Phase II of the project should establish a new performance level for image quality. Further, with the use of these algorithms, tissue beds currently inaccessible to ultrasound may become new areas for ultrasonic diagnoses. An example of this is the brain, where the extreme sound velocity in the skull reduces the potential for successful beam formation. The potential for successful commercial application of such instruments is significant.

Title of Project: Development of a Database on Unproved Cancer Treatments
Principal Investigator: Susan M. Ziemer
Awardee Organization: I.S. Grupe, Inc.
948 Springer Drive
Lombard, IL 60148
Telephone Number: (312) 627-0550
Awardee Number: 1 R43 CA44198-01

The objective of this program is to establish a method by which cancer treatments not being investigated through conventional channels can be identified, organized into a database, and disseminated to interested parties. Organizing this information will provide a means for identifying unscrupulous methods and allow those treatments with promise to be brought to clinical trials.

An immediate goal of this project is to classify treatments identified from reports in the open literature, including historical reports of folk remedies still in use and citations in popular literature being commercially exploited. In doing so, the mechanism for data collection and classification can be established, leading to a long-term goal of continuous monitoring and updating to include new data within the established hierarchy. In this way, a system for information related to new methods of combatting cancer can be set up. The methodology to be employed consists of (1) a comprehensive survey of the open literature during which search parameters for continued surveillance will be developed; (2) an analysis of the resultant material found pertinent from which the parameters for analysis will be established; (3) the generation of a database categorizing methods according to criteria such as source, type of treatment, and degree of success; and (4) specifications for the establishment of a distribution network.

Title of Project: Nutrition Information System for Consumer Education
Principal Investigator: Karen B. Levitan, Ph.D.
Awardee Organization: The KBL Group, Inc.
808 Pershing Drive, Suite 100
Silver Spring, MD 20910
Telephone Number: (301) 588-4633
Awardee Number: 1 R43 CA42652-01

The overall goal of this proposal is to develop a microcomputer-based, nutrition education, cancer prevention delivery system at the consumer level. This system will be installed in supermarkets and other stores to assist shoppers in point-of-purchase food decisions by allowing them to compare product brands based on factual nutrition information. The purpose of Phase I is to determine the feasibility of designing an interactive, microcomputer system providing nutrition information for consumer education (NICE). The prototype that will be developed during Phase II will provide shoppers with information on fiber and fat. Once it has been tested and debugged, it could be expanded to include information on other nutrients.

Title of Project: Clinicians' Knowledge System for Gastrointestinal Cancer
Principal Investigator: Lionel M. Bernstein, M.D.
Awardee Organization: Knowledge Systems, Inc.
1 Oak Brook Club Drive
Oak Brook, IL 60521
Telephone Number: (312) 834-0519
Awardee Number: 1 R43 CA42687-01

The specific aims of this project are to determine the feasibility of creating an integrated knowledge system that practicing physicians can easily and rapidly access for information from the medical literature needed to support their diagnostic and therapeutic decisions, and to assess the utility to physicians of such a system. The knowledge base will be a combination of core knowledge, derived from leading authoritative subspecialty textbooks, plus integrated updating of information from the current literature. It will be available online, accessible with a wide variety of terminals or microcomputers.

A natural language capability allows the physician to type an inquiry in natural English and quickly receive paragraphs provided in order of their ranked relevance to the query. The system also allows browsing within the hierarchical contents to find information providing different levels of detail, or to obtain contextual understanding.

The first integrated knowledge base will be on gastrointestinal cancer. Successful demonstration of its usefulness to physicians will lead to coverage of the larger fields of oncology and gastrointestinal disease, and finally to all of internal medicine. The commercial importance of this innovation lies in its potential for becoming the first routine source of knowledge acquisition for most practicing physicians.

Title of Project: Development of a Sleeve-Assisted Video Endoscope (SAVE)
Principal Investigator: William Z. Penland
Awardee Organization: Medac, Inc.
8900 Saunders Lane
Bethesda, MD 20817
Telephone Number: (301) 365-7614
Awardee Number: 1 R43 CA41914-01A1

Through semiautomated endoscopic investigation, Medac, Inc. plans to continue the development of a technique/device that will facilitate routine colonoscopic examination so that flexible sigmoidoscopy or total colonoscopy can be performed rapidly and painlessly by the general physician. This can expand the early detection of large bowel cancer and prevent its progression by permitting endoscopic removal of a premalignant precursor, the colonic polyp.

Medac, Inc. is investigating flexible sleeve and inflatable balloon cuff devices that are disposable and have the potential to move an endoscope in semiautomated fashion from anus to cecum. The device is moved back and forth along the endoscope in a repeating cycle of five steps under manual control. Low-pressure air is supplied by a control unit to the cuff for gripping and moving the colon wall.

Because of the simplified and uniform technique of endoscope advancement, this device will potentially make colonic endoscopy available to virtually all physicians. It will allow direct visualization and video recording/analysis of the epithelial surface of the entire large bowel. Mass screening for large bowel malignancy with minimum false-negative or false-positive results should be possible because of the high-resolution visualization of large bowel internal surfaces.

Title of Project: Continuously Variable Collimator for Radiation Therapy
Principal Investigator: Gabe F. Blosser
Awardee Organization: MedCyc Corporation
609 Beech Street
East Lansing, MI 48823
Telephone Number: (517) 351-1721
Awardee Number: 1 R43 CA45913-01

The goal of this research is to develop and test a new type of shaped-field collimator system to mount on existing oncology therapy linear accelerators and cobalt units. The collimator allows the radiation beam to be shaped in arbitrary irregular patterns to match the size and shape of the tumor so that the dose to the tumor region will be maximized relative to the dose received by surrounding normal tissue.

The shaping of the radiation field is achieved through an array of movable but permanently mounted tungsten rods, the position of the rods being set automatically by easy-to-fabricate styrofoam patterns. Medical technicians are relieved of the burden (and of the frequent minor injuries) associated with the handling of heavy cast-metal collimators, which are at present in frequent use for the shaping of irregular fields. The new "rod-type" collimator will reduce operating costs, improve staff working conditions, and increase the number of patients that a facility can handle.

The research plan involves collecting data on collimator attachment arrangements for four to six of the most frequently used therapy devices, designing collimators for these devices, performing life-cycle tests on critical elements, upgrading an existing prototype to fully automated status, and installing this prototype for weekend debugging periods on an existing therapy unit.

Title of Project: Synthesis of Antitumor Agents Related to Fredericamycin A
Principal Investigator: Michael T. Flavin, Ph.D.
Awardee Organization: MediChem Research, Inc.
9026 North Menard Avenue
Morton Grove, IL 60053
Telephone Number: (312) 226-7731
Awardee Number: 1 R43 CA45898-01

The objective of this Phase I proposal is to discover novel antitumor agents that may offer therapeutic advantages over those currently available. This research program will be based on the chemical synthesis of certain analogs of the antitumor antibiotic fredericamycin A. These analogs may possess greater potency, better drug delivery properties, and fewer side effects than the parent natural product. In addition, the analogs synthesized in this study may provide clues to the biochemical mechanism of action of fredericamycin A.

Title of Project: Facilitated Colonoscopy
Principal Investigator: Thomas W. Mix, D.Sc.
Awardee Organization: Merix Corporation
192 Worcester Street
Wellesley, MA 02181
Telephone Number: (617) 235-6630
Awardee Number: 1 R43 CA44191-01

Colonoscopy is well established as the definitive diagnostic procedure when malignancy of the large intestine is suspected. There is excellent evidence that all or nearly all colonic malignancy begins in previously benign polyps. If these could be removed while still benign, most colon cancer would be prevented. Colonoscopy, however, requires a high degree of skill to perform, is costly, and poses a risk of perforation of the colon. Discomfort to the patient can be significant as well, with anesthetics frequently required. The problems stem mainly from the difficulties of inserting the colonoscope, the most time-consuming and risky portion of the procedure.

A novel modification to colonoscopy is proposed for development which, if valid, would so facilitate colonoscope insertion as to revolutionize the procedure by reducing its time, risk, discomfort, and cost. The procedure could be offered as a screening study, drastically altering the risk of colon cancer. Phase I will demonstrate the new procedure in simulated colons, animal intestines, and finally in dogs. Clinical demonstration would be accomplished in a Phase II follow-up.

Title of Project: Cross-Linking Oligonucleotides for Chemotherapy
Principal Investigator: Rich B. Meyer, Jr., Ph.D.
Awardee Organization: MicroProbe Corporation
1725 220th Street, Southeast, #104
Bothell, WA 98021
Telephone Number: (206) 485-8566
Awardee Number: 1 R43 CA45905-01

Short oligodeoxynucleotides incorporating nucleotides modified by the addition of reactive cross-linking arms will be synthesized. These oligonucleotides should hybridize with target sequences in mRNA or DNA and, once bound, should covalently cross-link with the complementary sequence via the incorporated modified nucleotide.

In particular, derivatives of 4-aminopyrazolo(3,4-d)pyrimidine, with a haloalkyl or similar substituent in the 3-position, will be prepared. These derivatives are isosteric with a 7-substituted purine and should be capable of cross-linking with the 7-position of a purine in an adjacent base pair of the complementary strand.

This modified nucleoside will be converted into a blocked phosphoramidite and incorporated into an oligonucleotide on a DNA synthesizer. This oligonucleotide will be tested for covalent cross-linking to complementary and noncomplementary DNA restriction fragments. Such antisense, cross-linkable oligonucleotides, designed to minimize host toxicity, may be useful as chemotherapeutic agents for infectious diseases and cancer. They will be targeted at the mRNA or DNA of microorganisms or of any cancer tissue in which a rearranged oncogene is expressed.

Title of Project: DNA Probes to Detect Human Papillomavirus in Oral Cancer
Principal Investigator: Dennis E. Schwartz, Ph.D.
Awardee Organization: MicroProbe Corporation
1725 220th Street, Southeast, #104
Bothell, WA 98021
Telephone Number: (206) 485-8566
Awardee Number: 1 R43 CA45914-01

In situ DNA-probe hybridization assays will be used to determine the types of human papillomavirus (HPV) associated with oral cancers. Short, synthetic DNA probes, specific for HPV Types 6, 11, 16, 18, and 31, will be tested on thin sections of tumor specimens from the archives of the Division of Oral Pathology, University of Washington. The specimens will include papillomas and frank carcinomas.

This study will demonstrate the feasibility of routine testing of oral biopsies for HPV infection by *in situ* hybridization and may provide new information regarding the specific types of HPV associated with oral malignancy. In addition, this study will directly compare the efficacy of long, cloned DNA probes and short, synthetic DNA probes in *in situ* DNA hybridizations. The results of this project will be important for the commercial development of nonisotopic, DNA probe-based diagnostic systems for use in clinical and oral pathology laboratories.

Title of Project: Development of Surface Coils for Magnetic Resonance Imaging
Principal Investigator: James R. Domnanovich
Awardee Organization: Midwest Medical Technologies, Inc.
747 Cutter Lane
Elk Grove Village, IL 60007
Telephone Number: (312) 894-3171
Awardee Number: 1 R43 CA45883-01

The specific aim of this proposal is to develop a family of surface coils for magnetic resonance imaging (MRI). When surface coils are utilized, MRI images show improved spatial resolution and signal-to-noise ratios. High-resolution imaging of the central nervous system, extremities, and perhaps the coronary arteries will be possible with improved surface coil design. This would lead to improved diagnosis of cancers, trauma, and other diseases.

To detect the small radio-frequency signals used to form the MRI image, surface coil designs will: (1) maximize the organ-filling factor, (2) maximize receiver homogeneity, (3) maximize quality factor Q, and (4) minimize patient dielectric coupling. To realize these factors, parallel and series-parallel circuit designs will maximize Q by minimizing internal and external losses through distributed capacitances. Material research will be carried out to identify low-resistivity, low-dissipation factor components and coil materials. Coil geometries will be computer modeled to maximize the filling factor and reduce external coupling. Judicious choice of circuit/coil designs and materials will maximize Q, while matching coil impedance to MRI unit requirements for high signal-to-noise imaging. Bench testing and MRI imager evaluation will assess the coil-loaded Q, signal-to-noise ratio, and impedance matching to produce high-quality MRI images.

Title of Project: Tissue-Equivalent MRI Cardiac Phantoms
Principal Investigator: John A. Urbon, Ph.D.
Awardee Organization: Midwest Medical Technologies, Inc.
747 Cutter Lane
Elk Grove Village, IL 60007
Telephone Number: (312) 894-3171
Awardee Number: 1 R43 CA45908-01

Long-term objectives include: (1) development of an inexpensive, magnetic resonance imaging (MRI) tissue-equivalent material; (2) construction of MRI quality assurance standards; and (3) development of complex tissue-equivalent anthropomorphic MRI phantoms to aid in detection of pathological conditions. The first two goals will benefit the health care industry through the development of innovative technology, producing complex performance phantoms to aid in the assessment of new MRI diagnostic instrumentation and providing quality assurance for existing systems. Attainment of the third goal will help improve clinical diagnostic methods and lead to improved, lower cost patient care.

Goal attainment is predicated upon development of suitable MRI tissue-equivalent substances. Preliminary experiments indicate that gel-water composites, composed of a modified polysaccharide used in RF-microwave hyperthermia phantoms and appropriate modifying agents, show promise as MRI tissue equivalents. Phase I will involve systematic evaluation of the nuclear magnetic resonance (NMR) properties of this material using a 7- to 60-MHz-pulsed NMR spectrometer, construction of tissue-like composites, and the evaluation of composite imaging qualities and stability with a 0.5 Tesla MRI device. Concurrently, novel molding techniques to produce contiguous regions of dissimilar NMR will be examined.

Title of Project: Large-Scale Production of Avian Myeloblastosis Virus
Principal Investigator: Richard F. Piehl, Ph.D.
Awardee Organization: Molecular Biology Resources, Inc.
5520 West Burleigh Street
Milwaukee, WI 53210
Telephone Number: (414) 871-7199
Awardee Number: 1 R43 CA45876-01

Avian myeloblastosis virus (AMV), a source of reverse transcriptase for use in recombinant DNA work, is currently produced commercially from the plasma of leukemic chicks. Production involves inoculation of several hundred day-old chicks with AMV and harvest of virus-containing blood by heart puncture 7 to 10 days later. The research proposed will investigate the feasibility of commercial-scale production of AMV from cell cultures of chicken myeloblasts.

Procedures for *in vitro* transformation of chicken macrophage lineage cells with AMV and the *in vitro* growth of the transformed cells on a small scale are well known. Large-scale culture of AMV-transformed myeloblasts has also been achieved, but with specially constructed apparatus. The present proposal discusses adaptation of recent advances in cell culture conditions and apparatus for large-scale cell culture to production of AMV. Successful development of the cell culture method will give a procedure that is both more economical and more humane than the present *in vivo* method.

Title of Project: Conjugation of Small Ribosomal Inhibitors to Antibodies
Principal Investigator: Gowsala Pavanasasivam, Ph.D.
Awardee Organization: NeoRx Corporation
410 West Harrison Street
Seattle, WA 98119
Telephone Number: (206) 281-7001
Awardee Number: 1 R43 CA42613-01A1

NeoRx Corporation proposes a new series of small-molecular weight natural products that are similar to higher plant toxins in their mechanisms of action—inhibiting protein synthesis at the level of the ribosome. All inhibit *in vivo* translation in cell-free systems. Some are cytotoxic to eucaryotic cells at low concentrations (ID_{50} 100 pg/ml) and thus behave like the "intact" dimeric toxins ricin and abrin; others are not cytotoxic at relatively high concentrations (10 μg/ml) and are similar to ribosomal inactivating proteins (RIPs) such as gelonin. Monoclonal antibodies (MoAbs) are proposed as vehicles to facilitate binding and internalization of the noncytotoxic (RIP-like) molecules and to enhance selectivity of the cytotoxic (intact toxin-like) molecules.

Two of the RIP-like molecules, differing only in one site of acetylation, and one toxin-like molecule to an antimelanoma MoAb will be conjugated and tested for inhibition of protein synthesis and overall cytotoxicity and selectivity with antigen-positive and antigen-negative melanoma cells. Their conjugates may have equivalent potency but not suffer the poor delivery ceused by nonspecific uptake as occurs with higher molecular weight toxins. They are also not likely to suffer from drug-induced cross-resistance, as occurs with drugs currently used in

chemotherapy. Should either or both of these approaches prove feasible, it will be possible to construct several generations of a wide range of related antitumor agents that have unique mechanisms of action and that will be important new agents for the treatment of cancer.

Title of Project: Analysis of $Na_2B_{12}H_{11}SH$ for Neutron Capture Therapy
Principal Investigator: Jacalyn M. Schremmer
Awardee Organization: Nuclear Medicine, Inc.
900 Atlantic Drive. Northwest
Atlanta, GA 30318-5619
Telephone Number: (404) 873-6309
Awardee Number: 1 R43 CA42639-01A1

Nuclear Medicine, Inc. (NMI) intends to commercialize an alternate form of radiation therapy known as boron neutron capture therapy (BNCT). This therapy is currently and successfully being used in Japan to treat brain tumors. The Food and Drug Administration requires chemical characterization of $Na_2B_{12}H_{11}SH$, the pharmaceutical that makes the therapy possible, before it will approve clinical trials for BNCT in the United States.

NMI has obtained orphan drug status for $Na_2B_{12}H_{11}SH$ and proposes two different quantitative methods for measuring its purity: track-etch/thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC). The former method allows the sensitive measurement of the ^{10}B isotope in the boron polyhedron. Measurement by HPLC is based on analysis of the sulfhydryl group on $B_{12}H_{11}SH^{2-}$ by electrochemical or other means. The techniques thus complement one another and can be symbiotically applied to both chemical and biochemical analysis of boron-carrier compounds.

Title of Project: Pinpointing RNA Expression by *In Situ* Hybridization
Principal Investigator: Jack D. Love, Ph.D.
Awardee Organization: Oncor, Inc.
209 Perry Parkway, #7
Gaithersburg, MD 20877
Telephone Number: (301) 963-2500
Awardee Number: 1 R43 CA43349-01A1

Formalin-fixed, paraffin-embedded tumor tissue blocks from cancer patients are stockpiled in pathology labs throughout the world. These tissue blocks contain the secrets of oncogenes, their relationship to carcinogenesis, and their response to therapy. The overall aim of this proposed project is to determine the feasibility of developing *in situ* hybridization technology for detection of oncogene RNAs in these fixed tissues.

Phase I will take advantage of the fact that N-myc exhibits both elevated RNA expression and amplified gene copy number in neuroblastoma; neuroepithelioma will serve as a negative control. Together they provide a standardized system to evaluate the effects of various *in situ* hybridization conditions. Fresh tumor tissue will be obtained by propagating human cell lines in nude mice.

The most significant anticipated problem will be sensitivity. The use of RNA rather than DNA probes will allow for a posthybridization RNase treatment to reduce backgrounds and permit detection of RNA expression at very low levels in individual cells. Many of the current steps for *in situ* hybridization to frozen sections and cytospins do not give optimum results with fixed, paraffin-embedded sections. The various treatments work interactively to give an overall sensitivity level; therefore, a multidimensional array of tissue and slide treatments will be examined to maximize sensitivity.

Title of Project: A New Device for Microdosimetry
Principal Investigator: George S. Hurst, Ph.D.
Awardee Organization: Pellissippi International
10521 Research Drive, Suite 300
Knoxville, TN 37932
Telephone Number: (615) 675-9580
Awardee Number: 1 R43 CA45869-01

This proposal deals with the development of a radiation detector to make possible the direct measurement of the structure of charged-particle tracks in a gas. Such a detector will permit the measurement of microdosimetric distributions in volumes that correspond to nanometers in a biological cell, e.g., the diameter of a DNA molecule. When a charged particle penetrates a gas, electrons produced during ionization quickly become thermalized. The proposed detector would determine the positions of all of these electrons by imposing a suitable radio frequency field, causing the electrons to agitate and excite molecules of the gas, which would then fluoresce and produce photons that could be detected by an external optical detector. Thus, each point of light would represent the position of a single electron.

In Phase I, an experimental proof of concept will be made that a single charged-particle track could be detected optically. In Phase II, vidicon or other CCD detectors will be used to obtain spatially resolved images of all of the electrons produced in the track of a single charged particle.

Title of Project: Purification of Melanoma 250 Kd Tumor-Associated Antigen
Principal Investigator: Gary M. Stuhlmiller, Ph.D.
Awardee Organization: Piedmont Research Company
3508 University Drive, Suite 2
Durham, NC 27707
Telephone Number: (919) 968-0433
Awardee Number: 1 R43 CA44193-01

The goal of this project is to improve the existing purification procedure, developed by Piedmont Research Company, for the 250 Kd melanoma tumor-associated antigen (TAA) to allow production of adequate quantities of purified TAA for clinical evaluation. Purified TAA may prove an efficient agent for immunotherapy and for specific *in vitro* activation of patient T cells for subsequent therapy. Both the purification procedure and the TAA product will have commercial applications. Basic methodological approaches will include evaluation of alternative TAA solubilization procedures, use of immunoadherence chromatography, and evaluation of the destructive effects of endogenous protease activity.

Title of Project: Immunoassays for Mutagenic and Carcinogenic Adducts in Human DNA
Principal Investigator: Cynthia L. Sevilla, Ph.D.
Awardee Organization: Proteins International
1858 Star Batt Drive
Rochester, MI 48063
Telephone Number: (313) 852-1067
Awardee Number: 1 R43 CA45878-01

Difunctional carbonyl compounds are toxic, mutagenic, and carcinogenic and are ubiquitous contaminants of the human environment. The simplest examples of such compounds are malondialdehyde, acrolein, and methyl glyoxal. Malondialdehyde is a product of lipid peroxidation and prostaglandin biosynthesis and is present in virtually all mammalian tissues. Methyl glyoxal is also a natural product and is present in freshly roasted coffee. Acrolein is a major industrial starting material and is present in cigarette smoke. All of these compounds are mutagenic, and methyl glyoxal induces subcutaneous tumors when injected in mice.

The extent to which difunctional carbonyl compounds contribute to human cancer is uncertain, but there can be little doubt that exposure to these compounds is considerable. While it is thought that these compounds exert their mutagenic and carcinogenic effects by forming adducts with DNA, methods for accurate determination of these adducts are not available. The long-term goals of this project are the development of monoclonal antibodies specific for the major nucleic acid adducts of these difunctional carbonyl compounds, for use in enzyme-linked immunosorbent assays and in assays of spread DNA and DNA in nuclei. These assays will be developed for use in clinical and research monitoring of levels of these adducts in human DNA samples.

Title of Project: PC-Based Methods for Monitoring Ongoing Clinical Trials
Principal Investigator: Larry R. Muenz, Ph.D.
Awardee Organization: Quantech, Inc.
10101 Blue Tee Terrace
Gaithersburg, MD 20879
Telephone Number: (301) 977-3968
Awardee Number: 1 R43 CA45063-01

Phase III human oncology trials should be stopped as soon as possible if there is clear evidence that one treatment is superior to the others or that no treatment will emerge as superior. Quantech, Inc. proposes to study statistical methods for the early stopping of such trials and to implement these methods within a microcomputer package for interim clinical trial monitoring. In addition to a selection of group sequential methods for early stopping, the package will display ancillary data useful to statisticians, clinicians, and ethicists concerned with monitoring an ongoing study. By using commercial software for a distributed data system, remote sites will swiftly be able to enter and display critical outcome and toxicity data relevant to an early stopping decision.

The Phase I study will begin with a comparison, by computer simulation, of proposals for group sequential methods. Criteria to be compared include power, sample size at stopping, and the allocation of type I errors at each possible stopping point. The proposed methods will then be applied to real data from oncology trials to see if different methods might have led to different decisions. During Phase I, a computer system containing a variety of statistical features for interim monitoring of trials will be designed and implemented in a prototype system.

Title of Project: Photodynamic Therapy System with Singlet O_2 Dosimetry
Principal Investigator: Martin G. Cohen, Ph.D.
Awardee Organization: Quantronix Corporation
P. O. Box 9014
49 Wireless Boulevard
Smithtown, NY 11788
Telephone Number: (516) 273-6900
Awardee Number: 1 R43 CA45093-01

A system for photodynamic therapy (PDT) that provides, in addition to the therapeutic light dose, a method of real-time, intraoperative dosimetry will be assembled and demonstrated. In PDT, a parenterally administered photoactive dye (dihematoporphyrin ether, DHE) localizes in malignant tissue. Subsequent irradiation of the DHE-bearing tissue with light (630 nm) produces, in combination with oxygen, the cytotoxic reaction product, singlet oxygen ($^1O_2$). By monitoring the real-time-resolved $^1O_2$ fluorescence at 1.27 nm, a signal proportional to the $^1O_2$ production rate will result, thereby providing dosimetry information.

The system to be demonstrated employs a CW-pumped, Q-switched, frequency-doubled YAG laser driving a tunable dye laser emitting 70-nanosecond, 630-nanometer wavelength pulses at a 10-KHz rate. In addition to providing real-time dosimetry information, the system also allows for the study of a possible increase in the therapeutic effect due to the generation of the cytotoxic agent $^1O_2$ in "bursts." To date, the reciprocity of the PDT light dose does not appear to have been thoroughly investigated.

Finally, the inherent wavelength agility of a tunable dye laser makes this system useful with new photoactive dyes operating beyond 630 nm.

Title of Project: Computer-Controlled X-Ray Image Analyzer
Principal Investigator: Gerard J. Celitans, Ph.D.
Awardee Organization: Rad-Image Corporation
Box 382, 1633 Babcock
San Antonio, TX 78229
Telephone Number: (512) 772-4565
Awardee Number: 1 R43 CA43674-01

Rad-Image Corporation proposes to develop a portable, microcomputer-controlled scanning digitizer and auxiliary devices to measure: (1) x-ray target intensity distributions directly; (2) light intensity distributions from fluorescent screens, image intensifiers, and backlighted, developed x-ray films; and (3) kilovoltage, x-ray exposure, half-value layers, and time of exposure.

It is also planned to develop software to: (1) calculate and display, in 3-D graphics, optical transfer functions and modulation transfer functions from measured point-spread functions; and (2) characterize and calculate x-ray exposure parameters and predict x-ray image parameters. In addition, educational software to explain the physical basis of x-ray image theory will be developed.

The portable system will enable the imaging characteristics of an x-ray system to be measured rapidly *in situ* in the field at a level of sophistication found now only at advanced laboratory facilities and requiring substantial time. The increased knowledge of image parameters should improve the level of medical image quality and reduce patient radiation dose. The developed system will perform x-ray unit measurements now requiring several instruments, and it will use recent solid-state advancements in microcomputer hardware. It has significant potential in non-x-ray image systems because of its portability, ease of use, multifunction capability, and major cost savings compared to other instruments and methods.

Title of Project: Magnetic Object Detector for Pre-MRI Patient Screening
Principal Investigator: Lance McVay, Ph.D.
Awardee Organization: Resonant Images Company
11 Washington Avenue
Arlington, MA 02174
Telephone Number: (617) 648-5895
Awardee Number: 1 R43 CA45939-01

This research aims to establish the feasibility of a clinical device for detecting potentially hazardous magnetic objects inside the body of a patient who is about to undergo magnetic resonance imaging (MRI). Similar in usage to the walk-through devices used for library book secu-

rity, the detector will set up a magnetic field in a doorway. As the patient walks through, a receiving antenna will monitor the electromagnetic response of any objects.

Preliminary to the research, the technical literature will be thoroughly searched for material related to this type of detection. The major research effort will be to estimate the sensitivity of various detecting methods to small objects such as vascular clips.

Using computer simulations of the electromagnetic fields, the most promising technique will be theoretically identified. A prototype will be designed and its performance estimated. An experimental test of its effectiveness will be formulated.

Title of Project: *In Vitro* Screening Test for Detecting Antiestrogens
Principal Investigator: Arulasanam K. Thilagar, Ph.D.
Awardee Organization: SITEK Research Laboratories
12111 Parklawn Drive
Rockville, MD 20852
Telephone Number: (301) 984-2302
Awardee Number: 1 R43 CA45107-01

The overall objective of this proposal is to develop a reliable *in vitro* test system using human cell lines to screen compounds for their cytotoxicity and antiestrogenic activity.

Currently, a number of *in vitro* screening tests are used to identify potential chemotherapeutic drugs. Most of these tests utilize nonhuman (mostly rodent) cell lines that may not distinguish species-specific differences in toxicity of chemicals between humans and rodents. Although a few human cell lines (HT-29, A549, KB) are currently used to screen chemicals for their cytotoxicities, none of them are responsive to estrogens or antiestrogens Because in recent years patients with hormone-responsive solid tumors have been treated with both endocrine drugs (antiestrogens) and other chemotherapeutic agents, it is essential to develop an *in vitro* screening test with appropriate human estrogen-sensitive and estrogen-nonsensitive cell lines. Use of human cell lines will also be more relevant in view of the differences in the species-specific cytotoxicity of a number of compounds.

SITEK Research Laboratories proposes to develop a reliable protocol for a rapid, *in vitro* test using estrogen-responsive and estrogen-nonresponsive human cell lines. Such a test will be sensitive, relatively inexpensive, and allow the evaluation of a number of samples at the same time. In addition, the test will distinguish the toxicity caused by the antiestrogens from the nonspecific cytotoxicity or toxicity caused by other chemotherapeutic drugs.

Title of Project: Biochemical Control of Microcarrier Processes
Principal Investigator: William J. Hillegas, Ph.D.
Awardee Organization: SoloHill Engineering, Inc.
323 East William Street, Suite 44
Ann Arbor, MI 48104
Telephone Number: (313) 665-0453
Awardee Number: 1 R43 CA43352-01A1

Microcarrier systems show great potential for the large-scale growth of cells and the production of their metabolic products. SoloHill Engineering's long-term objective is to develop an improved microcarrier for growing fastidious, anchorage-dependent cells. The goal of this research is to understand the biochemical basis for the differences in cell growth and behavior ob-

served between several commercially available microcarriers and SoloHill Engineering's glass and collagen-coated microcarrier beads. The specific objective is to determine if the differences in the levels of endogenous proteolytic enzymes produced by cells on the various microcarrier substrates contribute to differences in cell growth and behavior on these substrates.

The Phase I objective will be to compare cell growth, cell morphology, and virus production by three types of commercially important cells—MRC-5, CEF, and MDBK—on various microcarrier substrates under normal growth conditions and under conditions in which the functioning of the enzyme is modulated. The microcarriers to be evaluated will be SoloHill Engineering's glass and collagen-coated beads and the several other commercially available substrates (Cytodex I and III, Ventregel, and Biosilon).

The results of these evaluations will aid in improving the glass and collagen-coated microcarrier beads and in developing more productive microcarrier protocols.

Title of Project: Large-Area, X-Ray-Sensitive Tube for Radiology
Principal Investigator: Milton Stoller
Awardee Organization: Spectrascan, Inc.
45 South Satellite Road
South Windsor, CT 06074
Telephone Number: (203) 528-9521
Awardee Number: 1 R43 CA45089-01

The proposed research is for the development and fabrication of a series of large-area, x-ray-sensitive video tubes, with 9-, 16-, and 25-inch diameters, for diagnostic radiology. If successful, the smallest tube will provide real-time imaging for dynamic studies, and all tubes will be capable of snapshot imaging. They will resemble television display tubes and are designed to provide high-resolution, wide-dynamic-range performance by electron beam read-out at the sensor target. Their design avoids the degradation in spatial resolution and loss of contrast in fluoroscopic-type systems that result from demagnification and veiling glare. They also lack the problems of solid-state imagers (such as the Fuji plate) associated with transport and read-out time. Furthermore, such tubes will make possible substantial reductions in the component and system costs of all photoelectronic systems available today.

Phase I will provide an analysis of all tube components and their functions for optimization of component selection and magnitudes. Phase II will develop and demonstrate feasibility with a prototype tube.

Title of Project: Light-Scan-Oriented Doppler Detection of Breast Cancer
Principal Investigator: Milton Stoller
Awardee Organization: Spectrascan, Inc.
45 South Satellite Road
South Windsor, CT 06074
Telephone Number: (203) 528-9521
Awardee Number: 1 R43 CA45918-01

The long-term objective of this project is to develop a practical methodology for early detection of breast cancer by combining the complementary nonionizing modalities of light scan and Doppler ultrasound. Light scan, in the context of this proposal, refers to the transillumination of the breast by red and near-infrared light, with examination of both absolute transmission and the ratio of transmission at the two frequencies. Such light scans can interrogate the breast volume for tissue that may be malignant to provide orientation for a second, nonionizing modality, Doppler ultrasound.

During Phase I, Spectrascan, Inc. will develop, through both mathematical simulation and experimentation, practical transducer designs for an ultrasound Doppler specifically suited to early detection of breast cancer. The electronic circuitry and computer software to implement a practical breast cancer-detecting Doppler for use in the clinical setting will be designed, constructed, and tested. A prototype system suitable for clinical testing combining light scanning and Doppler ultrasound will be designed and constructed.

In Phase II, clinical studies will be initiated to demonstrate the effectiveness of the combined modality in terms of the receiver-operating characteristics. The prototype system will be further refined to a practical unit suitable for commercial application.

Title of Project: Protein Kinase C Therapeutic Developmental Tools
Principal Investigator: Carson R. Loomis
Awardee Organization: Sphinx Corporation
3628 Carlisle Drive
Durham, NC 27707
Telephone Number: (919) 489-8473
Awardee Number: 1 R43 CA45866-01

The long-term goals of this research are to contribute to an understanding of the role of protein kinase C in neoplastic transformation and cellular regulation by signal transduction processes. Protein kinase C functions to transduce sn-1,2-diacylglycerol second messengers, produced in response to growth factors, neurotransmitters, hormones, and some oncogene products, and it is the receptor of tumor promoters. The hypothesis that protein kinase C may be the target of antitumor and other therapeutic agents will be tested by: (1) refining mixed micellar-assay methods to screen for protein kinase C agonists and antagonists and their mechanism of action; (2) applying these methods to the pilot testing of 500 compounds, submitted to NCI, that possess antitumor activity; and (3) refining methods of sn-1,2-diacylglycerol quantitation and applying them to normal and diseased tissues.

These studies are directly related to oncogenesis and antitumor therapeutic development programs. Importantly, such analyses will establish the desirability of biochemical prescreens of compounds submitted to the NCI and elucidate causative agents of cellular transformation. The central involvement of protein kinase C and sn-1,2-diacylglycerol second messengers is relevant to endocrinology, neurology, growth, differentiation, development, arthritis and other inflammatory responses, smooth muscle contraction, psoriasis, diabetes, and other human conditions.

Title of Project: Model-Scanner Validation for Inverse Scatter Imaging
Principal Investigator: Michael J. Berggren, Ph.D.
Awardee Organization: TechniScan, Inc.
1916 East Browning Avenue
Salt Lake City, UT 84108
Telephone Number: (801) 583-2679
Awardee Number: 1 R43 CA45852-01

TechniScan, Inc. proposes to test the effectiveness of a new ultrasound imaging method for the detection and screening of breast cancer with real data obtained from a scaled-down, working, scanner model featuring an electronically scanned transducer array. The complete transducer array will be a regular polygon constructed from four or six transducer arrays, each with 128 elements. Multiple transmitting and receiving multiplexer banks will allow strong incident fields to be produced and permit rapid data acquisition.

This design also provides high stability and freedom from vibration for the jitter- and drift-free data required for use in very accurate inverse-scattering imaging algorithms. These algorithms are based upon computing the inverse-scattering solution to the exact (not linearized) inhomogeneous Helmholtz wave equation. This

solution provides separate and independent images of density (ρ), compressibility (κ), and absorption (α). The spatial resolution of each of these three images is extremely high, near 250 microns or ⅛ wavelength at 3 MHz. Samples of breast cancer tissue, benign tumors, and other tissues will be scanned. This proof of concept will lead to construction of a full-scale scanner for Phase II clinical trials.

Title of Project: Ultrahigh-Resolution Magnetic Resonance Imager: NMR Microscope
Principal Investigator: John L. Delayre
Awardee Organization: Tecmag, Inc.
6006 Bellaire Boulevard, Suite 217
Houston, TX 77086
Telephone Number: (713) 667-1507
Awardee Number: 1 R43 CA44232-01

The goal of this project is to develop an Ultrahigh Resolution Nuclear Magnetic Resonance (NMR) Imager (*in vivo* NMR microscope) capable of a resolution of at least 10 microns. During Phase I, a set of gradient coils with a rise time of about 100 μs and an RF probe of reduced diameter (38 mm) will be developed to demonstrate the feasibility of the project. These components will be tested on the 33-cm bore NMR imaging spectrometer available at the University of Texas Medical School in Houston. Imaging of appropriate phantoms will be performed and the resolution assessed.

Title of Project: Epithermal Neutron-Beam Approach to Neutron Capture Therapy
Principal Investigator: John L. Russell, Jr., Ph.D.
Awardee Organization: Theragenics Corporation
900 Atlantic Drive, Northwest
Atlanta, GA 30318-5619
Telephone Number: (404) 873-6309
Awardee Number: 1 R43 CA42641-01A1

Theragenics Corporation has developed the first filter device to generate a deeply penetrating, high-flux, epithermal neutron beam free of significant fast neutron contamination. The device is a prototype of a therapeutic version intended for use in an alternative form of radiation therapy known as boron neutron capture therapy (BNCT).

The epithermal neutron beam will ultimately be coupled with a Theragenics Corporation orphan drug, $Na_2{}^{10}B_{12}H_{11}SH$, for the treatment of the extremely malignant brain tumor, glioblastoma multiforme. Upon Food and Drug Administration (FDA) approval of both the drug and device, radiation services will be offered that are much like those in radiation therapy and oncology departments in major hospitals.

Phase I consists of rebuilding and optimizing the prototype device for therapeutic purposes. Phase II involves extensive characterization of the resultant epithermal neutron beam, fulfilling FDA requirements for an Investigational Device Exemption (IDE) application. Phase II will then continue with two animal studies to assess the safety of the glioblastoma treatment. The results of these studies will finalize protocols for clinical trials of epithermal neutron beam BNCT.

Title of Project: Laser Catheter Ultrasonic Imaging System
Principal Investigator: William H. Newman, Ph.D.
Awardee Organization: Thermal Technologies, Inc.
P.O. Box 545, Kendall Square Branch
Cambridge, MA 02142
Telephone Number: (617) 577-1759
Awardee Number: 1 R43 CA43737-01A1

The goal of this project is to develop a prototype catheter-mounted ultrasonic transducer that could be used to direct laser surgery procedures that use light delivered through fiberoptic catheters. Laser surgery allows precise ablation of lesions such as tumors, atherosclerotic plaques, and vascular malformations at sites that are inaccessible by other techniques. However, it is also relatively easy to damage normal tissues adjacent to or underlying the lesions, or to cause perforations in hollow structures. These complications might be avoided with *in situ* diagnostic information about the character and thickness of the target tissues and the extent of thermal denaturation caused by the laser energy. Ultrasonic imaging, even when simple and one-dimensional, is more likely to provide this information than are optical or radiological techniques.

The specific aims of this Phase I proposal are to construct and evaluate a miniature ultrasonic transducer with a resolution of $<100\ \mu$ and an imaging depth >1 cm that could be combined with a side-emitting optical fiber to determine lesion thickness and to control ablation. The transducer will be tested in model systems and in animal and human tissues *in vitro*.

Title of Project: Scanned, Focused Ultrasound Hyperthermia System
Principal Investigator: Howard L. Resnikoff, Ph.D.
Awardee Organization: Thermo-Therapy Devices Corporation
One Cambridge Center
Cambridge, MA 02142
Telephone Number: (617) 225-2464
Awardee Number: 1 R43 CA44188-01

Hyperthermia, alone or in combination with chemotherapy and/or radiation, is rapidly emerging as an effective modality for cancer therapy. It is generally agreed that among the currently available techniques, scanned, intensity-modulated ultrasound (SIMFU) has the best potential for localized heating of deep tumors in most anatomical locations. Based on clinical results obtained from approximately 200 cancer patients at the Harvard-MIT Hyperthermia Center with the prototype SIMFU research system, there is considerable demand for a clinical SIMFU system with comparable performance.

Using the well-documented SIMFU system as the basic model, the major goal of this Phase I project is to investigate the feasibility of designing a commercially viable, scanned, focused ultrasound hyperthermia system that is cost effective, can be routinely administered in the clinical setting, is capable of treating a wide variety of tumors, and is reliable and upgradable. The existing SIMFU hyperthermia system currently in use at the Hyperthermia Center has evolved developmentally over the last 10 years in a research environment. Consequently, it is complex, costly, and difficult to operate. Phase I funding is required to develop the specifications necessary for standardized clinical use.

National Institutes of Health
National Cancer Institute

Title of Project: *In Vitro* Test of Intestinal Toxicity of Anticancer Drugs
Principal Investigator: M. Guillaume Wientjes, Ph.D.
Awardee Organization: Trini Laboratories
2287 Palmleaf Court
Worthington, OH 43085
Telephone Number: (614) 424-5232
Awardee Number: 1 R43 CA44227-01

Intestinal toxicity is a major side effect of cancer chemotherapy. The procedures to isolate and culture rat small intestinal, epithelial crypt cells, which are the target cells for drug toxicity, have recently been developed. The overall objective of this study is to establish an *in vitro* method to quantify the *in vivo* intestinal toxicity of anticancer drugs. The Phase I study will examine the feasibility of using an *in vitro* toxicity assay to predict the intestinal toxicity of anticancer drugs using the rat as an animal model. The research plan is to evaluate and correlate the drug-induced rat intestinal crypt-cell toxicity *in vitro* and the intestinal disturbances in intact animals.

Two antimetabolites, 5-fluorouracil and methotrexate, have been selected as the test drugs. Drug toxicity will be determined by the concentration as well as the duration of exposure to the drug. To make a valid comparison of the *in vitro* and *in vivo* toxicities, the *in vitro* and *in vivo* studies will be done under similar drug concentration-time (AUC) profiles. The crypt cytotoxicity and the intestinal disturbances, observed under the same AUC of the drug, will be compared, and a qualitative and quantitative correlation will be sought.

The Phase II study will examine the general applicability of the *in vitro* assay using at least three drugs from each of the major drug classes, including antimetabolites, alkylators, and DNA reacting agents, and will compare the rat and human cells. Comparison of the cytotoxic responses of rat and human crypt cells is necessary to understand the applicability and limitations of the crypt cytotoxicity assay to predict for drug toxicity in patients.

Title of Project: Triangular SPECT Scanner and High-Sensitivity, 3-Dimensional, Dynamic Radionuclide Imaging
Principal Investigator: Chun B. Lim, Ph.D.
Awardee Organization: Trionix Research Laboratory, Inc.
1666 Enterprise Parkway
Twinsburg, OH 44087
Telephone Number: (216) 425-9055
Awardee Number: 1 R43 CA45094-01

The objective of this proposal is to develop a highly optimized single-photon emission-computed tomography (SPECT) system for 3-dimensional (3-D) brain and torso organ imaging with dynamic capability. The specific aim is to design, develop, and test a triangular SPECT scanner based on three rectangular NaI(T1) gamma cameras of 16-inch × 9-inch FOV for high-sensitivity SPECT. Sensitivity improvement will be 450 percent for brain by matched fan beam collimation, and 300 percent for body organs, over the current single-head systems, and the current 30-minute imaging time will be reduced to 7 to 10 minutes. Another major aim is to develop 3-D mapping capability of rCBF by continuous clockwise (CW) and counterclockwise (CCW) rotation for full-projection data collection in each 120 degrees, with time resolution down to 5 seconds.

This camera-based system allows collimator design flexibility for resolution-sensitivity tradeoff. For the brain, three detectors make a tight triangle with 10-inch diameter FOV imaging volume. For torso organs, the three detectors follow the body contour orbit for best resolution. For fast dynamic imaging, three detectors rotate continuously CW and CCW with the reversing time less than 1 second. This drastic reduction of SPECT imaging time is particularly important for very sick patients and for pediatric imaging.

Title of Project: Liposome-Encapsulated B-10 for Neutron Capture Therapy
Principal Investigator: Paul G. Schmidt, Ph.D.
Awardee Organization: Vestar, Inc.
939 East Walnut Street
Pasadena, CA 91106
Telephone Number: (818) 792-6101
Awardee Number: 1 R43 CA44208-01

Neutron capture therapy is an attractive alternative to standard radiation techniques for cancer treatment if nuclei, such as ^{10}B, can be selectively concentrated in tumors. Small, unilamellar, phospholipid vesicles are known to be taken up by animal and human tumors. Liposome formulations will be tested for their ability to encapsulate high concentrations of boron compounds in a stable manner. Biodistribution of these B-containing liposomes will be tested in mice bearing EMT6 tumors with radiolabeled $Na_2 B_{10} H_{10}$.

Title of Project: Expert Radiology Assistant
Principal Investigator: Kris A. Dines, Ph.D.
Awardee Organization: XDATA Corporation
6115 Allisonville Road
Indianapolis, IN 46220
Telephone Number: (317) 251-0933
Awardee Number: 1 R43 CA45915-01

Feasibility research is proposed for the development of a computer-based expert radiology assistant (XRA) to aid in the diagnosis of breast cancer. The proposed expert system has the potential to assist radiologists in the interpretation of diagnostic images and clinical data using artificial intelligence. The system was formed by encoding in the computer software the knowledge of human experts. The system will assist in the diagnosis of difficult cases and provide ready access to the knowledge of experts, leading to increased distribution and application of mammographic expertise.

Specific aims of Phase I are designed to provide experimental evidence to test the capability of an expert system to make diagnoses based upon clinical and image descriptors provided by radiologists. A prototype system will be implemented and tested using verified clinical cases to aid in the discovery of reasoning methods and data descriptors that constitute sufficient knowledge to make diagnoses at expert levels of performance.

Having defined a sufficient set of image descriptors, a Phase II effort will concentrate on full implementation of the interactive image-understanding portion of the system, integration of the diagnostic and image analysis subsystems, expansion of the knowledge base, and definitive clinical testing.

Phase II Grants

Title of Project: Proton Accelerator for Medical Applications
Principal Investigator: Ronald L. Martin, Ph.D.
Awardee Organization: ACCTEK Associates, Inc.
901 South Kensington
LaGrange, IL 60525
Telephone Number: (312) 354-4529
Awardee Number: 2 R44 CA41218-02

The long-range goal of this program is the development and commercialization of proton accelerators suitable for radiation therapy of cancer in hospital or clinical settings. These can provide beams of protons up to 60 nA at 250 MeV in a smaller version of the accelerator. A larger version will produce helium ions to 250 MeV/μ, or with lower magnetic field, 250 MeV protons from H^- acceleration and charge-exchange extraction for precision current control. The latter could make possible the use of raster scanning beams of protons for delivery to the patient, reducing the size and cost of the gantry and significantly improving radiation treatment.

The Phase I effort completed the conceptual design and cost estimate for these accelerators. The Phase II program will construct models of the magnets designed, assemble them in a section of a ring, and conduct a series of experimental demonstrations with an H^- beam injected from a 300 KeV preaccelerator, including simulated charge-exchange extraction with feedback current control.

These Phase II efforts will demonstrate the commercial feasibility of the design concepts. Phase III will make commercial units available.

Title of Project: Mullerian Inhibiting Substance
Principal Investigator: Richard L. Cate, Ph.D.
Awardee Organization: Biogen Research Corporation
14 Cambridge Center
Cambridge, MA 02142
Telephone Number: (617) 864-8900
Awardee Number: 2 R44 CA42340-02

Mullerian Inhibiting Substance (MIS), a product of the fetal testis, is a 70 Kd glycoprotein that initiates regression of the Mullerian duct, the anlagen of the uterus, fallopian tube, and upper vagina. Biogen Research Corporation has shown that this fetal protein can also inhibit the growth of some tumors derived from cell types that respond to the fetal regressor in embryonic life. Thus, MIS may prove to be an effective treatment for gynecologic tumors. However, the human protein is very rare.

During Phase I, the human MIS gene was isolated and expressed in animal cells, providing the technology for producing large amounts of human MIS. In Phase II, it is proposed to test the efficacy of MIS as an anticancer drug, scale up production of recombinant MIS, and conduct preclinical tests. Specifically, studies during the first year will focus on purifying small amounts of MIS (10 mg) and demonstrating antiproliferative effects against tumors *in vitro* in tissue culture and *in vivo* in animals. During the second year, large amounts of MIS will be produced and purified (10 g) for preclinical testing.

The results of this research will provide the basis for filing an Investigational New Drug (IND) application and permit the commencement of clinical trials in humans.

Title of Project: Quantitation of Estrogen-Receptor Concentration in Cells
Principal Investigator: James W. Bacus, Ph.D.
Awardee Organization: Cell Analysis Systems, Inc.
261 Eisenhower Lane South
Lombard, IL 60148
Telephone Number: (312) 629-6611
Awardee Number: 2 R44 CA42700-02

The objective of this project is to develop quantitative, estrogen-receptor concentration measurements using high-resolution, digital-image microscopy techniques. These techniques will enable direct measurements of receptor concentrations in tissues and cells. This is an improvement over current biochemical assays, which give only an average value for receptor concentration in homogenized specimen samples containing varying proportions of malignant cells. The proposed assay will measure both the concentration of receptors in cell populations and the proportion of cells in the tumor population that have estrogen receptors above a certain concentration level.

The recent development of monoclonal antibodies against estrogen receptors makes the development of methods for immunocytochemical localization of estrogen receptors feasible. Additional recent advances in quantitative-imaging cytology can be combined with this to develop a fast, efficient, and more accurate assay method and to eliminate the subjective visual components of the method. This new quantitative assay will be especially useful in diagnosing and treating patients with tumors containing estrogen receptors, as they have a higher probability of responding to hormonal therapy and seem to have a better prognosis than patients whose tumors do not contain this receptor.

Title of Project: Early Detection of Ovarian Carcinoma
Principal Investigator: Vincent R. Zurawski, Jr., Ph.D.
Awardee Organization: Centocor
244 Great Valley Parkway
Malvern, PA 19355
Telephone Number: (215) 2[illegible]3-4488
Awardee Number: 2 R44 CA40945-02A1

This Phase II proposal is designed to provide and analyze a database that will largely delineate the feasibility of pursuing a Phase III study of the CA 125 immunoradiometric assay (IRMA) as a component of strategy aimed at early detection and diagnosis of ovarian cancer in an at-risk population. Specific objectives will include: (1) accurate determination of the specificity of the test for ovarian cancer used one time and serially in a study population of 5,000 women aged 40 years or older, (2) determination of the nature of apparent false-positive results of this test, (3) identification of possible confirmatory tests that will improve the specificity of the CA 125 IRMA for ovarian cancer, and (4) preliminary retrospective estimates of the sensitivity of the CA 125 IRMA for occult ovarian cancer.

The principal endpoints of this study will be: (1) a plan to proceed to a prospective study of 50,000 or more women to determine accurately the sensitivity and positive predictive value of the CA 125 IRMA and associated confirmatory and adjunctive tests for the early detection of ovarian carcinoma in an at-risk population, and (2) a collection of data allowing for determination of the cost effectiveness of such a screening strategy. The results of this study should also provide a model for future evaluation of serum assays for such purposes and establish a well-characterized serum bank for evaluation of such assays.

National Institutes of Health
National Cancer Institute

Title of Project: Engineering of Antibody-Binding Sites to Tumor Antigens
Principal Investigator: James S Huston
Awardee Organization: Creative BioMolecules, Inc.
35 South Street
Hopkinton, MA 01748
Telephone Number: (617) 435-3001
Awardee Number: 2 R44 CA39870-02

Basic methodology and genetic elements will be developed for the production of biosynthetic antibody-binding domains of interchangeable specificity. V_H and V_L domains based upon the Fv region of an antidigoxin antibody will be refashioned to have the hypervariable segments of an antiprotein antibody. This is intended to alter its specificity without the need to remake the constant framework of the Fv. This hybrid of two different murine monoclonal-binding regions will be expressed in prokaryotic and eukaryotic hosts to permit purification of renatured V_H, V_L, and recombined Fv. Analysis of its binding properties will determine if it functions entirely as planned, and if not, computational and physicochemical studies will provide the basis for redesign.

Similarly, the constant framework of a human Fv region will be used to support the binding site from a murine antiprotein monoclonal. Such intrachain, interspecies hybrids could offer unique advantages for human therapy. In particular, minimization of a human immune reaction to a murine-binding site is desirable, as is utilization of murine monoclonal structural features that are experimentally accessible. Attempts will be made to fuse V_H and V_L genes into a single Fv gene via a linker that will be compatible with normal refolding and recombination of component domains. This single polypeptide-chain-binding site will be useful for immunotargeting biologically active proteins.

Title of Project: Statistical Software for Exact Analysis of Categorical Data
Principal Investigator: Cyrus R. Mehta, Ph.D.
Awardee Organization: Cytel Software
137 Erie Street
Cambridge, MA 02139
Telephone Number: (617) 661-6990
Awardee Number: 2 R44 CA36681-02

CYTEL Software intends to produce and market a statistical software package for exact nonparametric inference on a broad range of problems commonly encountered by applied statisticians. The emphasis is on providing a computationally efficient, strong, and portable set of tools for performing exact inference whenever large sample assumptions justifying conventional asymptotic inference are in doubt. This happens often with contingency tables that are characterized by empty cells or cells with small entries. Exact methods for analyzing these "sparse" contingency tables, while preferred, cannot be applied because they have not been incorporated into any of the commercial statistical packages. This gap in commercially available software is not an oversight. Formidable technical difficulties are encountered when attempting to produce software for exact inference. Several major innovations in the theory of statistical computing have been published recently by the principal investigator and co-investigator. As a result, exact statistical inference is now a practical proposition for most important types of contingency table data. CYTEL Software will integrate these innovations into a stand-alone statistical package for mainframe, mini-, and microcomputers. The package will interface in a friendly way with popular commercial statistical packages such as SAS, BMDP, and SPSS, and with Lotus 1-2-3, a popular microcomputer spreadsheet.

Title of Project: Microcomputer-Assisted Procedures for Cytogenetics
Principal Investigator: Kerry B. Clark, Ph.D.
Awardee Organization: Genetics Data Services, Inc.
3150 South Babcock Street, Suite O
Melbourne, FL 32901
Telephone Number: (305) 768-2048
Awardee Number: 9 R44 CA47005-02

The development of a microcomputer-based, chromosome analysis system is proposed, which will enable a trained cytogeneticist to analyze clinical chromosome preparations more efficiently. The system will allow the trained cytogeneticist to make all decisions regarding chromosome recognition and identification of chromosome defects. The computer will aid the cytogeneticist in assembling final karyotypes from video images digitized directly from the microscope. The system will produce permanent pictorial records of karyotypes and will provide laser disk archiving for chromosome analyses of patients, allowing nearly instantaneous retrieval of chromosome data.

This approach to interactive chromosome analysis should greatly increase the speed with which clinical results can be obtained, ease the fatigue that is associated with chromosome analysis directly from the microscope, relieve the burdens on the trained cytogeneticist associated with photographic documentation, and facilitate automated chromosome data archiving and information retrieval.

Because of the high level of microcomputing power used in Phase I of this project, Genetics Data Services, Inc. will also incorporate into its system mitotic cell finding/evaluation and computer-aided instruction in karyotyping. Opportunities for commercialization associated with this project are very significant, as there are approximately 400 laboratories in the United States performing clinical chromosome analysis, and a smaller but significant number involved in cytogenetics research.

Title of Project: SAR Estimation of Carcinogenesis Bioassay Results
Principal Investigator: Kurt Enslein
Awardee Organization: Health Designs, Inc.
183 East Main Street
Rochester, NY 14604
Telephone Number: (716) 546-1464
Awardee Number: 2 R44 CA37494-02A2

The long-term goal of this research is to make available to the chemical community methods for the estimation of toxicity endpoints, especially carcinogenicity. Several aims are included in the research under this grant: (1) enhancement of the carcinogenicity database; (2) development of a global carcinogenicity equation; (3) further refinement of the NCI/NTP assay-based carcinogenicity equations for heterogeneous as well as more closely related sets of chemicals; (5) development of organ-specific oncogenicity equations for 10 organ systems or sites; (6) development of equations for carcinogenic potency for heterogeneous and more closely related data sets; and (7) development of carcinogenicity equations for closely related series of chemicals based on NCI/NTP, pharmaceutical, and CFR 21 data.

Independent parameters will include physicochemical parameters such as log P, molar refractivity, and molecular area and volume. Other parameters will include molecular connectivity indexes and MOLSTAC® substructural descriptors. Statistical methodology will be based on discriminant analysis; multiple, particle, and ridge regression; and principal component analysis.

Title of Project: Diagnostic Probes to Unique Epitopes on Amylase Isozymes
Principal Investigator: Michael P. Woodward, Ph.D.
Awardee Organization: Humagen, Inc.
1500 Avon Street Extended
Charlottesville, VA 22901
Telephone Number: (804) 979-4000
Awardee Number: 2 R44 CA40860-02

Monoclonal antibodies specific for each of the three amylase isoenzymes—salivary, pancreatic, and ovarian—will permit a more accurate assessment of the cause of hyperamylasemia. Current methods for measuring total amylase activity in serum are inadequate, while those for isozyme analysis are either indirect or time consuming.

During Phase II, Humagen, Inc. intends to utilize antisalivary-specific and antipancreatic-specific monoclonal antibodies as the basis for a diagnostic kit that will permit the direct determination of serum amylase levels. In brief, immobilized monoclonal antibody will be used to capture the appropriate amylase isoenzyme. During Phase II, this kit will be rigorously tested and compared with the Phadebas IsoAmylase kit, which has FDA approval.

Elevated serum levels of an ovarian amylase show a good correlation with serous-type ovarian cancer. During Phase II, monoclonal antibodies specific for ovarian amylase will be generated. These antibodies will be used to monitor the amylase activity in serum, cyst tissue, and/or fluid and compared with CA 125 reactivity of patients having ovarian cancer. These monoclonal antibodies will form the basis for a diagnostic kit that can be used to monitor recovery from or recurrence of ovarian cancer.

Title of Project: A Reliable Test for Gastrointestinal Lesions
Principal Investigator: Paul J. Lawrence, Ph.D.
Awardee Organization: Litmus Concepts, Inc.
3485-A Kifer Road
Santa Clara, CA 95051
Telephone Number: (408) 245-5525
Awardee Number: 2 R44 CA44213-02

Fecal occult blood tests (FOBT) are routinely used to detect the blood released from GI lesions, including colorectal cancer. Colorectal cancer is the second most common serious cancer in the United States with 130,000 new cases and 60,000 deaths annually. Because it is slowly progressive with a long asymptomatic period, colorectal cancer provides an ideal opportunity for early detection and therapy. It is known that colorectal cancers frequently bleed, and that appropriate FOBT can be important aids to early detection.

Unfortunately, many clinical studies indicate that the most widely used commercial FOBT suffers from serious limitations in sensitivity and specificity. Proposed alternatives are no longer simple, rapid, inexpensive clinical tools.

The proposed research is designed to produce the best commercial embodiment of a technically superior FOBT with significantly improved clinical performance while maintaining key user advantages.

Title of Project: DNA Probes for Detection of Chromosomal Translocations
Principal Investigator: Gordon Foulkes, Ph.D.
Awardee Organization: Oncogene Science, Inc.
222 Station Plaza North, Suite 330
Mineola, NY 11501
Telephone Number: (516) 877-2882
Awardee Number: 2 R44 CA40868-02

A specific chromosomal abnormality, the Philadelphia translocation, is characteristic of leukemic cells in over 95 percent of all patients with chronic myelogenous leukemia. The Philadelphia chromosome, generated by this translocation, is the result of a break occurring within the bcr gene on chromosome 22; sequences 3′ of the breakpoint are translocated to chromosome 9, from which the c-abl oncogene is transferred into the bcr gene. The resulting chimeric bcr-c-abl gene produces a chimeric mRNA and abnormal abl protein. Four bcr homologous loci have been molecularly cloned and characterized in Phase I research. In addition, three different abl homologous sequences have been isolated.

The primary objective of this project is to determine the possible involvement of bcr and abl homologous sequences in human cancer. In Phase II, the chromosomal location of the bcr-related genes will be determined and cDNAs will be isolated from those loci found to be actively transcribed genes. Probes isolated from the cDNAs will be used to screen DNAs from leukemias, lymphomas, and solid tumors for rearrangements and translocations; pulsed-field, gradient gel electrophoresis may be used as an alternative separation method for large DNA fragments. In each instance where the association of a member of the bcr or abl gene family with a malignancy can be established, DNA probe tests will be formatted for application as clinical diagnostic tests.

Phase I Contracts

Title of Project: Feasibility Demonstration of an Automatic Solubility-Monitoring System
Principal Investigator: Kam C. Lau, Ph.D.
Awardee Organization: Automated Precision, Inc.
7901-C Cessna Avenue
Gaithersburg, MD 20879
Telephone Number: (301) 948-7986
Awardee Number: 1 N43 CM73730-00

A program to demonstrate the feasibility of an automatic, laser-scanning solubility-monitoring system is proposed. The system is designed to replace current manual solubility-testing procedures performed in government laboratories, pharmaceutical companies, and food industries with a more economical and efficient procedure.

Phase I efforts will be directed to the designing, construction, and demonstration of key subsystems of the proposed system. These include a compact material handler, a high-precision weighing stage, a laser-scanning solubility-monitoring system, and a control and data processing system. Phase I provides an opportunity to explore alternative systems and to define the functional requirements and design criteria for an advanced, automatic, solubility-monitoring system to be developed in Phase II.

Title of Project: Multidrug-Resistance Patterns in Human Tumor Cells
Principal Investigator: Jeffrey F. Lemontt, Ph.D.
Awardee Organization: Integrated Genetics, Inc.
31 New York Avenue
Framingham, MA 01701
Telephone Number: (617) 875-1336
Awardee Number: 1 N43 CM73717-00

New antitumor compounds identified in screening programs are frequently ineffective against metastatic human tumors that exhibit multiple-drug resistance. To enhance the efficiency of screening for agents likely to be effective in the treatment of such tumors, Integrated

Genetics, Inc. proposes to develop a diagnostic product consisting of a panel of well-characterized, multidrug-resistant derivatives of human tumor cell lines, following selections for resistance to actinomycin D, adriamycin, colchicine, daunorubicin, vinblastine, or vincristine. The panel will be useful as a direct, initial screen for compounds active against tumors having different spectra of *de novo* or acquired resistance to these commonly used chemotherapeutic agents.

During Phase I, an established, malignant, melanoma cell line will be propagated with stepwise selection for increasingly higher levels of resistance to each drug listed above. Each of the six sublines will then be tested for their relative levels of resistance to all six drugs. Preliminary molecular characterization of these multidrug-resistant sublines will be restricted to a determination of the presence or absence of common amplified DNA or RNA sequences by hybridization to a defined cDNA probe (homologous to a common, amplified gene from Chinese hamster cells).

During Phase II, multidrug-resistant sublines of other human tumor cell lines from different neoplastic tissues (e.g., carcinomas of small lung cells, breast, colon, kidney, etc.) will be selected and tested for common amplified DNA sequences.

Title of Project: Polyhydroxyphenyl Derivatives Designed for Antitumor Activity
Principal Investigator: Bart van't Riet, Ph.D.
Awardee Organization: Molecules for Health, Inc.
3313 Gloucester Road
Richmond, VA 23227
Telephone Number: (804) 644-8591
Awardee Number: 1 N43 CM73716-00

The reductive conversion of ribonucleotides to deoxyribonucleotides, catalyzed by ribonucleotide reductase, is a crucial and rate-limiting reaction in the DNA biosynthetic pathway. This reaction, therefore, represents a logical target for cancer chemotherapy. In response to the need for an effective agent at this site, a series of ribonucleotide reductase inhibitors, based on a vicinal polyhydroxyphenyl structure, has been developed. The compound of the initial series with the best antitumor activity in animal tumor models, Didox, has entered human clinical trials.

The purpose of this proposal is to develop an even more effective agent of this type. Specifically, Molecules for Health, Inc. will add substituents to known active structures in seven classes of polyhydroxyphenyl compounds to enhance binding on the enzyme. Structural requirements for optimum activity will be evaluated. To accomplish this, Molecules for Health, Inc. will measure the degree of enzyme inhibition, the rate of free radical scavenging (mechanism of inhibition), and the antitumor activity in the L1210 leukemia model. Additionally, the National Cancer Institute will be provided with adequate quantities of the most promising compounds for further antitumor testing. An improved understanding of structural features will give direction to further development. Successful compounds resulting from Phase I will undergo pharmacokinetics and toxicological evaluation in Phase II.

Phase II Contracts

Title of Project: Assay for Predicting Methotrexate Sensitivity in Human Breast Cancer
Principal Investigator: Adeline J. Hackett, Ph.D.
Awardee Organization: Aeron Biotechnology, Inc.
3023 Summit Street
Oakland, CA 94609
Telephone Number: (415) 835-9039
Awardee Number: 1 N44 CM77826-00

The long-range goal of this proposal is to develop an *in vitro* test to improve selection of therapies for individual breast cancer patients by predicting response to methotrexate. Existing assays for breast cancer cells cannot determine methotrexate sensitivity because of requirements for feeder layers and medium components that can rescue sensitive cells. This proposal will, therefore, evaluate two different approaches: (1) improving an existing clonogenic assay by manipulating a serum-free medium based on MCDB 170, so that methotrexate toxicity is achieved; and (2) developing a totally different assay for methotrexate resistance that measures uptake of fluorescein-conjugated drug using a fluorescence-activated cell sorter (FACS). The latter assay does not require clonal growth.

Phase I will establish the necessary medium formulation for the clonal assay and show that methotrexate dose-response curves are feasible for normal and tumor-derived epithelial cells. Additionally, Phase I will continue the FACS studies and expand potential sources of clinical material and correlations so that during Phase II, both assays may be continued and evaluated for efficacy and practicality. The assays developed in Phase I will provide a means to isolate methotrexate-resistant cells; their mechanisms of resistance will be examined during Phase II. Thus, these *in vitro* assays will not only be useful for predicting patient sensitivity testing, but should also provide a basis for improved drug design.

Title of Project: Information Resource Activities in Chemoprevention Literature
Principal Investigator: Caroline C. Sigman, Ph.D.
Awardee Organization: CCS Associates
1285 Hamilton Avenue
Palo Alto, CA 94301
Telephone Number: (415) 328-7876
Awardee Number: 1 N44 CN75524 00

The objective of this project is the development of a comprehensive information resource on chemoprevention that may be applied to the identification of chemopreventive agents and to other research and development problems in chemoprevention. The development of chemopreventive agents is a high-priority research effort at NCI, particularly for agents that are efficacious and safe for use in patients at high risk for developing certain types of cancers.

A primary result of Phase I of this project was the development of a master list database of 543 potential chemopreventive agents, with indicators of efficacy and literature references. The information on efficacy incorporated into this database was that information judged to be most useful to NCI in prioritizing agents for further study.

In Phase II, the master list database will be updated, and databases of efficacy test results (animal bioassays, short-term tests, epidemiology, intermediate markers) and toxicity will be developed for the agents included in the master list. These databases are expected to be applied to various aspects of research and development planning for both NCI and commercial clients. Potential applications include structure-activity studies, establishing testing priorities, and evaluating the reliability of various testing protocols.

Title of Project: Phased-Array Applicator System for Deep-Tissue Hyperthermia
Principal Investigator: A.Y. Cheung, Ph.D.
Awardee Organization: Cheung Laboratories, Inc.
10000A Aerospace Road
Lanham-Seabrook, MD 20706-2217
Telephone Number: (301) 794-8933
Awardee Number: 1 N44 CM77838-00

Phased-array systems have been tested to indicate that the SAR pattern can be altered by a proper combination of phase and amplitude controls of the incident electromagnetic waves. Microstrip patch radiators will be made by Cheung Laboratories, Inc. Under a subcontract to the City of Hope National Medical Center, dosimetry studies and software development will be conducted for a phased-array integrated system to be developed by Cheung Laboratories, Inc.

Microstrip applicators of single- and multiple-patch arrangements will be tested on phantoms made of simulated brain, fat, muscle, and bone tissue in realistic shapes of the human head, neck, extremities, chest, and abdomen. Four frequencies will be used: 13.56, 300, 433, and 915 MHz. SAR patterns will be measured using a digital thermographic system. The power-generating system will be automated to control the phase and amplitude of the applied power to each applicator to achieve desired heating patterns. Software will be integrated into the final system for clinical applications.

Title of Project: A Portable and Extended Version of MLAB
Principal Investigator: Barry Burow, Ph.D.
Awardee Organization: Civilized Software, Inc.
7735 Old Georgetown Road, Suite 410
Bethesda, MD 20814
Telephone Number: (301) 652-4714
Awardee Number: 1 N44 CM77811-00

MLAB, a modeling laboratory, is a uniquely powerful, very high-level, mathematical and graphical programming language. It is extremely valuable to the research community at NIH and other biomedical research institutions. However, MLAB runs only on DEC-10/20 computers because it is written in the SAIL language, uses a special graphics package written in DEC-10 Macro-Assembler, and is tightly bound to the DEC-10/20 operating system. During Phase I, Civilized Software, Inc. carefully studied the problem of converting MLAB and devised a strategy for converting MLAB to a portable form, which includes various enhancements and considers the important issue of graphics.

Civilized Software, Inc. proposes to convert the MLAB interpreter into a portable form to make it more widely available and to enable it to survive the eventual demise of the DEC-10/20 computer. A portable version of MLAB will be produced in the C language and will include functional implementations on several personal computer systems. GRAPHX, a replacement for the Omnigraph graphics package, will also be built. In addition, documentation for the operation of the portable MLAB will be developed.

This effort will result in the creation of the following marketable products: (1) a complete, portable MLAB system, including manuals; and (2) a high-quality graphics package, including text in multiple fonts, 2- and 3-dimensional graphics, and terminal independence. The program will be suitable for general purpose and CAD/CAM applications.

Title of Project: High-Performance, Class AB Pulse-Amplifier Design for MRI
Principal Investigator: F. David Doty, Ph.D.
Awardee Organization: Doty Scientific, Inc.
600 Clemson Road
Columbia, SC 29223
Telephone Number: (803) 788-6497
Awardee Number: 1 N44 CM77804-00

The proposed work is intended to reduce the cost of magnetic resonance imaging (MRI) by developing superior, low-noise, low-cost, class AB pulse amplifiers with substantially lower initial and operating costs. Novel transformer geometries and materials were demonstrated in Phase I for reducing leakage and lead inductances to 10^{-9} H while maintaining adequate mutual inductance

for broadband use from 5 MHz to 140 MHz, at pulse powers up to 5 KW. Novel nonsaturating 200 W bipolar rf power circuits, offering improved reliability and performance from 5 MHz to 150 MHz, were also tested during Phase I, and work on very high-density, high-efficiency, 12 KW 80 KHz, switching-power supplies was begun.

Phase II will involve total system integration and prototype manufacturing of 5 KW class AB pulse amplifiers for MRI, while continuing to advance the state of the art in low-loss binders for high-power carbonyl iron powder transformer cores. Completed 5 KW pulse amplifiers are expected to cost much less than comparable class A amplifiers.

Title of Project: Cloning of Human Tumor Cells in Tissue Culture Systems
Principal Investigator: Martin J. Murphy, Jr., Ph.D.
Awardee Organization: Hipple Cancer Research Corporation
4100 South Kettering Boulevard
Dayton, OH 45439-2092
Telephone Number: (513) 299-7120
Awardee Number: 1 N44 CM77829-00

During Phase II of this contract, Hipple Cancer Research Corporation will exploit the unique merits and advantages of the capillary cloning of human tumor cells for both basic tumor cell biology exploration and in the identification of investigational new drugs with putative anticancer properties. Prototypic automated optical systems for tumor colony counting and characterization, data analysis, and data storage will be developed. Coded investigational new drugs from the Drug Development Branch of the National Cancer Institute and from pharmaceutical companies will be used to test and develop the capillary human tumor clonogenic assay as a screening tool for potentially active anticancer agents.

Title of Project: *In Vitro* Antineoplastic Drug Toxicology Characterization
Principal Investigator: Martin J. Murphy, Jr., Ph.D.
Awardee Organization: Hipple Cancer Research Corporation
4100 South Kettering Boulevard
Dayton, OH 45439-2092
Telephone Number: (513) 299-7120
Awardee Number: 1 N44 CM77831-00

In this Phase II contract, the development and standardization of *in vitro* clonogenic assays for hematopoietic precursor cells in glass capillaries and Petri dishes will be completed. Using these assays for erythroid (BFU-e and CFU-e), myeloid (CFU-gm), and megakaryocytic (CFU-meg) precursors, investigational new anticancer and anti-AIDS agents will be screened for potential clinical bone marrow toxicity using mouse, canine, and human marrow as target cells.

Title of Project: Biochemical Monitoring of Pesticides and Solvents with Supercritical Fluid Chromatography
Principal Investigator: Douglas W. Later, Ph.D.
Awardee Organization: Lee Scientific
4426 South Century Drive
Salt Lake City, UT 84123
Telephone Number: (801) 261-2300
Awardee Number: 1 N44 CP71086-00

The detection and characterization of pesticides, industrial solvents, and their metabolites in body fluids and tissues are important for evaluating the potential long-term health effects of exposed populations. Current chromatographic methods for the analysis of these materials in biological systems are tedious, time consuming, complex, or nonspecific and lacking sensitivity. The primary objective of this project is to evaluate capillary supercritical fluid chromatographic (SFC) techniques for biological-monitoring analysis of pesticides, industrial solvents, and their metabolites of interest to NCI. These compounds are generally polar and thermally labile, and capillary SFC promises to be advantageous for their analysis.

In Phase I, methods were developed using various supercritical fluids and capillary-column stationary phases for the separation of several chlorinated and phosphonate pesticides, selected metabolites, and acrylonitrile solvent. In Phase II, capillary SFC methods will be expanded for the analysis of pesticides and industrial solvent residues in body fluids, tissue, and excreta of rats or mice. Additionally, the potential chemical insult of these materials to mammalian genetic material will be investigated in DNA-binding studies. These studies will result in the expanded development of capillary SFC methods that can be used to assess exposure effects of pesticides and industrial solvents in human populations.

Title of Project: Development of Catheters with Integrated Fiberoptic Temperature Sensors
Principal Investigator: Mei H. Sun, Ph.D.
Awardee Organization: Luxtron Corporation
1060 Terra Bella Avenue
Mountain View, CA 94043
Telephone Number: (415) 962-8110
Awardee Number: 1 N44 CM77841-00

The overall objective of this project is to develop a commercially viable system for fast, accurate, on-line measurement and control of tissue temperatures during microwave-induced interstitial hyperthermia, as used in cancer therapy. In Phase I, the feasibility of instrumenting an interstitial catheter with multiple rf-immune fiberoptic sensors located in the wall of the catheter without significantly increasing catheter size was demonstrated. This design leaves the bore free for insertion of the microwave antenna, places the sensors in better thermal contact with the tissue being heated, and makes possible an on-line assessment of the temperature distribution along the length of the antenna during treatment.

Phase II has two major subgoals: (1) further improvement of the catheter and sensor materials and design to allow cost-effective volume fabrication and assembly; and (2) evaluation and preliminary development of a cost-effective instrument capable of supporting a large number of multisensor catheters. Prototype catheter evaluation will also include extensive animal and clinical testing.

Title of Project: Noncharring, Hemostatic, Surgical Laser System
Principal Investigator: Irving Itzkan, Ph.D.
Awardee Organization: Medical Laser Research & Development Corporation
46 Clark Street
Malden, MA 02148
Telephone Number: (617) 322-8693
Awardee Number: 1 N44 CM77832-00

The aim of this program is to develop a surgical laser system that can remove tumors or other tissues with precision, minimal blood loss, and minimal damage to adjacent tissue. The Phase I program was a demonstration of laser control parameters required for hemostatic action with minimal adjacent tissue damage in a murine model *in vivo*. Phase II will include demonstra-

tion of laser scalpel action, operator interface design, and system integration, providing a prototype surgical laser system. Demonstration of the efficacy of this system will include acute and long-term (wound healing) studies *in vivo*. Currently available surgical laser systems produce char and hemostasis or no char and no hemostasis. The surgical laser system proposed herein provides hemostasis while making clean, sharp cuts with no char formation and minimal adjacent tissue damage.

Title of Project: Early Detection of Extravasation of Intravenous Cytotoxic Drugs
Principal Investigator: Kenneth L. Carr
Awardee Organization: Microwave Medical Systems, Inc.
South Avenue, Building 7, M/S-704
Burlington, MA 01803
Telephone Number: (617) 272-3000
Awardee Number: 1 N44 CM77821-00

Intravenous or intra-arterial administration of liquids, such as oncotherapeutic drugs, commonly use a hollow needle or catheter inserted into a superficial artery or vein. However, patient movements can dislodge the needle/catheter and permit an accumulation of liquid in the perivascular tisssue, with concomitant discoloration, discomfort, and possibly extensive destruction of tissue. Currently, detection of this condition requires sufficient infiltration of liquid to produce pain, swelling, discoloration, or cessation of liquid administration due to the build up of liquid pressure within the local tissues.

The Phase I study proved the feasibility of passive, noninvasive, microwave radiometry for the early detection of extravasation. Data indicate that the detectability of extravasation increases with flow rate, with difficulty experienced at flow rates <20 ml/hour with room temperature fluids. Also, detectability increases as fluid temperature decreases and detectability appears independent of the diameter of the i.v. cannula. The proposed program, taking full advantage of the positive results of Phase I and consistent with objectives provided by the health care industry, will lead to the development and prototype evaluation of a low-cost, compact instrument suitable for the early detection of extravasation. Antenna configurations evaluated in Phase I indicate the feasibility of a disposable low-cost, conformal, printed-circuit antenna. The development of this antenna will be completed in Phase II.

Title of Project: Chemical Synthesis of Radiolabeled Antitumor Agents
Principal Investigator: Josef Moravek, Ph.D.
Awardee Organization: Moravek Biochemicals, Inc.
577 Mercury Lane
Brea, CA 92621
Telephone Number: (714) 990-2018
Award Number: 1 N44 CM77830-00

In this Phase II project, the synthetic approaches to labeling of selected compounds of interest to NCI will be developed to secure efficient methods for their preparation. The proposed compounds are: acetaldehyde dimethylacetal-1-C^{14}, N-(p-azido-3,5-H^3-benzoyl)-N′-β-aminoethylvindesine, N-(p-azido-3-I^{125}-salicyl)-N′-β-aminoethylvindesine, 4-azidobenzoate-(3,5-H^3)-N-OH-succinimidyl ester, 4-azido-(3-I^{125})-salicylate-N-OH-succinimidyl ester, N-(p-azido-3,5-H^3-benzoyl)-deacetylcolchicine, N-(p-azido-3-I^{125}-salicyl)-deacetylcolchicine, N-(p-azido-benzoyl)-deacetylcolchicine, N-(p-azido-salicyl)-deacetylcolchicine, 2-azidoadenosine-8-H^3, 3′-azido-3′-deoxythymidine-methyl-H^3, L-buthionine sulfoximine-3,4-C^{14}, cyclopentenylcytosine-5-H^3, cyclopentenyluracil-5-H^3, deacetylcolchicine, deoxycytidine-6-H^3, 5-deoxy-myo-inositol-5-H^3, 2′,3′-dideoxyadenosine triphosphate-2,8-H^3, 2′-3′-dideoxycytidine triphosphate-5-H^3, etoposide-C^{14}(VP-16-C^{14}), 5-fluorouracil-β-d-arabinofuranoside-6-H^3, L-histidinol-2-C^{14}, *l*-L-leucovorine-3′,5′,7,9-H^3, *l*-L-methyltetrahydrofolate-3′,5′,7,9-H^3, phosphoribosyl glycinimade-(glycine-C^{14}), 2-thiophene carboxaldehyde-(carbonyl-C^{14}), and teniposide-C^{14}(VM 26-C^{14}).

Title of Project: Computer-Controlled, Multileaf Collimators for Radiation Treatment Accelerators

Principal Investigator: Gerald Entine, Ph.D.
Awardee Organization: Radiation Monitoring Devices, Inc.
44 Hunt Street
Watertown, MA 02172
Telephone Number: (617) 926-1187
Awardee Number: 1 N44 CM77842-00

One of the most important criteria for successful radiation therapy is the ability to deliver the highest possible tumor dose while minimizing the dose to normal tissue. Most techniques currently used for shaping radiation therapy beams involve the fabrication of custom-made, dense alloy blocks. While these blocks have proven to be relatively effective, their construction is labor intensive and expensive. They are also poorly suited to dynamic radiation therapy or to more than a few treatment portals.

Due to recent advances in computerized control systems, it should now be feasible to develop a computer-controlled, multileaf collimator for use in both static and dynamic radiation therapy. Such a device could be made to fit into the brackets currently used to hold the alloy blocks and thus be compatible with existing machines and protocols.

Radiation Monitoring Devices, Inc., in collaboration with the Massachusetts General Hospital, conducted a Phase I research program that demonstrated the feasibility of this approach. It is therefore proposed to complete the research and to construct a working clinical prototype. Such a system should provide a significant advancement in the quality of radiation therapy by providing more effective shaping of radiation therapy portals and by making possible the shaping of the portals during arc therapy.

Title of Project: Thermal-Dissipative Mechanisms for Tumor Hyperthermia

Principal Investigator: William H. Newman, Ph.D.
Awardee Organization: Thermal Technologies, Inc.
One Kendall Square, Box 545
Cambridge, MA 02142
Telephone Number: (617) 577-1759
Awardee Number: 1 N44 CM77855-00

Determination of thermal dosimetry for the evaluation of noninvasive and interstitial hyperthermia applicators for large, deep-seated tumors requires adequate local and dynamic tissue thermal property data. These include tissue temperature, thermal conductivity, thermal diffusivity, and blood flow data. The objective of this project is to develop and market a portable, self-contained, modular clinical instrument for the local, simultaneous quantification of tissue thermal properties and blood flow (perfusion) in small tissue volumes.

The project's specific aims are to: (1) verify by experiment the thermal model obtained in Phase I; (2) establish experimentally the ability to quantify perfusion accurately at low levels by a single measurement, eliminating the requirement for a no-flow calibration procedure; (3) optimize the instrumentation capabilities for perfusion measurements, both transient and continuous, at these low levels; and (4) distribute and perform field testing and evaluation of the instrument under clinical conditions in selected hyperthermia research facilities.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Phase I Grants

Title of Project: Development of a Controlled-Environment Chamber
Principal Investigator: Gary R. Papas
Awardee Organization: American Boremene, Inc.
53 East Rogues Path
Huntington, NY 11746
Telephone Number: (516) 673-3333
Awardee Number: 1 R43 HD22736-01

The long-term objective is to develop a mechanical device that will provide complete environmental control (temperature, pressure, humidity, sterility, pH, gaseous atmosphere, and light rays) for biological or industrial specimens under microscopic examination. Controls will be maintained even during periods of physical manipulation of the specimen and during microscopic observation through optically clear lenses inherent in the design of the device.

American Boremene, Inc. will work with North Shore University Hospital to develop this device. The aim is to develop a functional device from a prototype. Specifically, the environmentally controlled chamber will be used for the incubation of and complete control over a particular specimen: fertilized mammalian ovum. Methodology will include designs based on mechanical engineering and physical principles, consideration of existent technology, and responsiveness to input from the medical sector. The device will be tested as to its ability to maintain environments against current laboratory techniques with experiments involving *in vitro* fertilization of mice.

There is no technology that provides for complete environmental control in an economical format that can be easily managed on the stage of a microscope. Commercial applications that will result from successful research include an increase in the accuracy and efficiency of any experiment requiring environmental control, a means of protecting researchers from hostile organisms or noxious materials, an improvement in the success rate of human *in vitro* fertilization, and energy-cost reduction during the cracking of petroleum.

Title of Project: An Immunoassay for a Human Growth Hormone Variant
Principal Investigator: Thomas R. Anderson, Ph.D.
Awardee Organization: Berkeley Antibody Company, Inc.
4131 Lakeside Drive, Suite B
Richmond, CA 94806
Telephone Number: (415) 222-4940
Awardee Number: 1 R43 HD23061-01

The objective of this research proposal is to develop antibodies capable of distinguishing normal human growth hormone (hGH-N) from the product of the variant growth hormone gene (hGH-V). Peptides will be synthesized corresponding to regions of dissimilarity from both forms of the hormone. These peptides will then be conjugated to carrier molecules for synthesis of effective immunogens and used to generate specific antibodies in rabbits. These antibodies will be tested for specificity of binding to one form of the hormone or the other. Such antibodies will be useful to determine whether or not the variant gene is expressed in humans. Immunoassays utilizing these hormones will have extensive utility for the diagnosis of growth disorders in humans.

Title of Project: Colorimetric Measurement of Milk Progesterone
Principal Investigator: Willfried Schramm, Ph.D.
Awardee Organization: BioQuant of Ann Arbor, Inc.
912 North Main Street
Ann Arbor, MI 48104
Telephone Number: (313) 995-2176
Awardee Number: 1 R43 HD22316-01A1

In this project, the feasibility of a novel, solid-phase, colorimetric assay will be investigated; monoclonal antibodies will be covalently immobilized on glass as the solid matrix. Several chemical reactions will be studied to identify linkages that give low nonspecific binding of proteins and small molecules while maintaining the integrity of immunoglobulins. Glass will be chemically refined to obtain a uniform, reproducible coat of antibodies independent of the physical history of glass and batch-to-batch variation. A new conjugate, hapten-biotin, will be evaluated with streptavidin-enzyme as a tracer for colorimetric quantification.

The resulting solid-phase assay will be implemented initially for measurement of progesterone in milk of cows. BioQuant of Ann Arbor, Inc. intends to develop a simple, reliable assay for monitoring estrous cycle, ovarian cyclicity postpartum, ovarian dysfunction, and pregnancy in dairy cows. A practical procedure to measure progesterone concentration in milk outside a laboratory setting also has substantial economic value in cattle breeding.

Phase I of this project will establish the feasibility of such a method and Phase II will be devoted to subsequent development of an assay that can be performed under field conditions by nontrained personnel.

Title of Project: Solid-Phase Assay for Saliva
Principal Investigator: Willfried Schramm, Ph.D.
Awardee Organization: BioQuant of Ann Arbor, Inc.
1919 Green Road
Ann Arbor, MI 48105
Telephone Number: (313) 995-2176
Awardee Number: 1 R43 HD22371-01A1

The long-range goal of this research is to develop a device incorporating an assay for simple, quick, reliable, accurate, and highly sensitive measurements of compounds in human saliva. Phase I feasibility research is focused on development of the solid-phase assay portion with progesterone as the prototypic analyte. The primary application of the progesterone assay will be for the assessment of fertility status in women (follicular *vs.* luteal phase of the menstrual cycle *vs.* pregnancy). Technologies resulting from development of the proposed product will also provide the basis for adapting the assay to other biological media (e.g., equine, bovine, and porcine saliva) to facilitate economic domestic animal breeding and, with different antibodies, to detect other substances. The initial assay will utilize an existing, highly specific monoclonal antibody to progesterone in blood plasma. The proposed system will be evaluated and optimized with a radiolabeled indicator, but highly sensitive alternatives for a colorimetric assay meeting the same quality criteria will be explored and implemented in parallel as progress allows.

The unique collection/assay device to be developed in Phase II is designed to remove food particles, eliminate problems with endogenous salivary mucins, and rapidly yield readily visualizable colorimetric differences. Once feasibility of the approach is proven, separate projects will be undertaken to adapt the technology to quantitation of other compounds and agents (e.g., street drugs, corticoids, toxins, and therapeutic drugs).

Title of Project: Expression Vectors for Secreted Human Estrogen Receptor
Principal Investigator: Phyllis A. Ponte, Ph.D.
Awardee Organization: California Biotechnology, Inc.
2450 Bayshore Frontage Road
Mountain View, CA 94043
Telephone Number: (415) 966-1550
Awardee Number: 1 R43 HD22659-01

The long-term goal of the research is to obtain a Chinese hamster ovary cell line capable of producing human estrogen receptor as a significant amount of its secreted protein. Purified receptor protein may then be used (1) to obtain X-ray crystallographic data on the structure of the receptor to aid in rational anti-estrogen drug design, and (2) to act as a research reagent for the development of estrogen antagonists for treatment of estrogen receptor tumors.

The specific aim of the proposal is the production of a mammalian cell expression vector capable of encoding a secreted estrogen receptor and the production of CHO cell transfectant pools using this vector. A primary accomplishment will be the invention of expression vectors allowing for the rapid construction and *in vitro* analysis of any novel secretory protein.

Title of Project: Sex Selection in Embryo Transfer
Principal Investigator: Stephen S. Wachtel, Ph.D.
Awardee Organization: Center for Reproductive Biology
Spring Creek Ranch
380 South Collierville-Arlington Road
Collierville, TN 38017
Telephone Number: (901) 853-7601
Awardee Number: 1 R43 HD21838-01A2

It is proposed to devise serological methods for routine identification of male and female bovine embryos, with a view to the control of sex ratio during commercial embryo transfer. Embryos will be exposed to newly developed monoclonal antibodies directed against male-specific H-Y antigen and then to goat antimouse-Ig bearing the fluorescent dye, FITC. The embryos will be scored for labeling under a fluorescent microscope. Early indications are that the method is effective and atraumatic. If this is substantiated by cytogenetic analysis and pregnancy tests, further work will be directed to the development of a kit that can be used regularly in embryo transfer and to the development of systems that combine sexing and cryopreservation.

Improvement of the bovine gene pool is limited by low reproductive rates and by the 6-year interval between generations. The major benefit of embryo transfer is in the increased reproductive efficiency of valuable breeding stock. Sex selection would have a significant impact on the embryo-transfer industry by increasing reproductive efficiency still further: Dairy farmers and breeders in general might prefer to transfer female embryos and to use male embryos for research, cryopreservation, or direct implantation for fattening.

Title of Project: A Formal Approach to Teaching Children Decision-Making Skills
Principal Investigator: Rex V. Brown, Ph.D.
Awardee Organization: Decision Science Consortium, Inc.
7700 Leesburg Pike, Suite 421
Falls Church, VA 22043
Telephone Number: (703) 790-0510
Awardee Number: 1 R43 HD23071-01

Personalized decision analysis (PDA), based on the maximization of subjective expected utility, is academically well established as a normative model of decision making. Practitioners working on real decisions have recently developed variants that have proven to be useful prescriptive tools for professional decision makers. Based on cognitive and educational psychology research, it is hypothesized that, with some adaptation, these tools can be taught to middle school children and enhance their informal decision-making skills throughout their lives. It is proposed to validate that hypothesis by designing course material, exercising it in two or three schools in the Washington and Philadelphia areas, and testing its efficacy on simulated decision tasks.

Specific student skills to be enhanced include: internalized patterns of thinking that underlie everyday decisions; major personal decisions requiring deliberate analysis; participation in controversial public decisions; contributing to family decision processes; and counseling others. Scientific advances in prescriptive decision theory and pedagogical theory are expected.

Title of Project: Machine-Aided Task-Training System
Principal Investigator: Roy P. Sallen
Awardee Organization: Design Automation, Inc.
809 Massachusetts Avenue
Lexington, MA 02173
Telephone Number: (617) 862-8998
Awardee Number: 1 R43 HD23070-01

This program addresses the application of computer-controlled electronic and mechanical equipment in the vocational training of mentally retarded persons. Proposed is a research and development effort to embody the training-system concept in modular hardware and software for versatile manual workstations. The modules, in conjunction with other specialized vocational materials, can be readily adapted to training assistance in a broad variety of tasks involving such basic skills as attending, counting, accurate placement of items, packaging, and in-seat behavior. Configuration of a workstation and system programming for training on specific task sequences can be accomplished by instructors without experience in computers or electronics. Each training setup provides for the automatic acquisition of data that tracks client performance and progress.

As a first step in implementing the system and evaluating it in a realistic setting, a basic workstation will be assembled. It will be used initially to assist in training clients in the fabrication of memo pads, a present vocational activity of one of the many ongoing programs now serving handicapped persons in Massachusetts. The proposed workstation will be evaluated at that program with the help of the existing clients and staff.

Title of Project: Item Development and Pilot Testing of the MAP-Screen
Principal Investigator: Lucy Jane Miller, Ph.D
Awardee Organization: Developmental Technologies
4857 South Albion Street
Littleton, CO 80121
Telephone Number: (303) 770-4818
Awardee Number: 1 R43 HD22670-01

Developmental Technologies proposes to develop the MAP-Screen, a short screening test to determine which preschool-aged children are at risk for learning disabilities. The MAP-Screen will be developed from the research of the Miller Assessment for Preschoolers (MAP), a more comprehensive, predictive instrument, and serve as a companion product to the MAP.

The MAP-Screen is being proposed in direct response to requests from publishers and consumers to develop a product that would be as reliable but shorter in length and less expensive. Comprehensive item selection will occur to meet recognized psychometric standards for test development and practical considerations. Item selection will be based on: extensive, previous

item research and predictive validity, test-retest, and reliability coefficients for each item; cost; administration time; and marketing considerations. The resulting pool of items will be pilot-tested on 160 Colorado children (N=120 normal, N=40 at risk) and data on estimates of item difficulty and discrimination will be analyzed. In Phase II, the MAP-Screen will be nationally standardized on a sample of 3,200 children stratified by age (2 to 6 years), race, sex, and socioeconomic status according to U.S. Census statistics. Manufacturing and marketing will be undertaken by a major publishing firm.

Title of Project: Computerized Assessment of Maternal and Infant Nutriture
Principal Investigator: Monica Bank Epstein
Awardee Organization: Diet-Tek, Inc.
P.O. Box 6505
Falls Church, VA 22046-0987
Telephone Number: (703) 556-0909
Awardee Number: 1 R43 HD23443-01

Diet-Tek, Inc. will develop a prototype microcomputer-based system to assess maternal and infant nutritional status and track changes in status following intervention. Assessments will be unique for pregnant and lactating women and adolescents, and full-term and preterm infants. Programming tools will be evaluated and used to build a system with the capability to change reference standards used in crucial calculations without the user having knowledge of computer programming. The resultant system will reduce the time clinicians spend performing tedious calculations while providing additional data that will aid in diagnosis, intervention, and maintenance of both healthy and ill infants.

In Phase I, a prototype computer system for the prenatal and postnatal nutritional assessment of females and their infants will be developed. A functional analysis will be conducted, followed by development of a limited prototype system. Identification of all data to be included in the system will be made.

In Phase II, complete system development, including some expert system capabilities and detailed beta-site testing by pediatric and obstetric practitioners and nutritionists, will be accomplished. Any modifications to the prototype system will be made. Phase III will consist of marketing the system.

Title of Project: Computerized Sperm Motion Analyses—Clinical Trials with a New Prototype
Principal Investigator: Neil B. Goldman
Awardee Organization: The Fertility Testing Laboratory
330 South 9th Street
Philadelphia, PA 19107
Telephone Number: (215) 829-5042
Awardee Number: 1 R43 HD23067-01

Sperm motion analyses and automated semen analyses are presently being performed by computerized systems. However, these systems are expensive ($35,000-$45,000) and they are not cost effective for most laboratories. Furthermore, it is still unclear whether the measurements that are derived from these systems have clinical relevance. At The Fertility Testing Laboratory, a new prototype system for sperm motion analysis and automated semen analysis has been developed which has comprehensive research capabilities in its basic design, but it has been streamlined for practical clinical use. This system measures sperm density, percent motility, instantaneous velocity, curvilinear velocity, net velocity, progressiveness ratio, and course direction change. Course direction change is a new measurement that allows recording the angular changes of the sperm tracks on a frame-to-frame basis. Planned research will continue with the prototype system by examining a variety of clinical specimens from infertility patients and do-

nors, and analyzing these data with statistical analysis routines incorporated into computer software. These clinical trials will help develop a marketable system, and provide us with data to move forward into Phase II to study other new aspects of motion analysis, flash photography, and harmonic analysis.

Title of Project: Applied Embryology Techniques in Nonhuman Primates
Principal Investigator: Steven A. Voelkel, Ph.D.
Awardee Organization: Helix International Corporation
635 Louisiana Avenue
Baton Rouge, LA 70802
Telephone Number: (504) 387-1112
Awardee Number: 1 R43 HD21861-0102

This project is the first phase of a long-term, joint venture between Helix International Corporation and the University of Southwestern Louisiana to establish a colony of monozygotic nonhuman primate twins for biomedical research models and to develop the technology and in-house expertise for initiating work in interspecies embryo transfer in endangered primates.

During the course of this research, a nonsurgical embryo-recovery technique will be perfected for recovery of uterine-stage embryos from rhesus monkey (*Macaca mulatta*) females. Recovered embryos (morula to blastocyst stages) will be microsurgically bisected into monozygotic twin demi-embryos (DE). The DE will be used to compare two culture systems (CMRL medium alone or with cocultured endometrial fibroblasts) for maintaining *in vitro* viability over 24 hours. Following culture, the DE will be stained with fluorescein diacetate to assess viability. The DE will then be fixed and stained to count the number of cells or frozen for subsequent assessment of viability following cryopreservation.

Ultimate success in producing a substantial colony of monozygotic nonhuman primate twins will provide uniquely valuable animal models for biomedical research.

Title of Project: Continuous Intrapartum Fetal pH, pO_2, pCO_2, Temperature, and ECG
Principal Investigator: Howard M. Hochberg, M.D.
Awardee Organization: International Biomedics, Inc.
1631 220th Avenue, Southeast
Bothell, WA 98021
Telephone Number: (206) 485-2200
Awardee Number: 1 R43 HD23445-01

International Biomedics, Inc. will develop and prove a fetal spiral scalp probe for continuous intrapartum monitoring (CIM) of ECG, pH, pO_2, pCO_2, and temperature. This will provide labile fetal data (ECG, blood gases) and other data reflecting the totality of recent metabolic insults (pH, temperature). The utility of CIM of fetal ECG and pH sampling is well known. The literature indicates that the CIM of pO_2, pCO_2, and fetal-maternal temperatures may be of value, and it is believed that they can be used to detect improper probe placement. The complete CIM data should enhance the reliability of fetal diagnosis and therapy.

International Biomedics, Inc. has developed and evaluated a CIM spiral ECG/tissue pH probe in a 300-patient, Investigational Device Exemption (IDE) controlled study for the Food and Drug Administration. In addition, a 430-micron-diameter, multiparameter (MP) intravascular probe for pO_2, pCO_2, pH, and temperature is being tested. During Phase I, the MP system will be adapted to the needs of CIM, and the bench, toxicology, and instrument qualification studies will be completed. During Phase II, a subcutaneous pouch and fetal animal studies will be performed in pigs to quantify the subcutaneous probe data versus arterial and venous data. Later in Phase II, IDE-controlled clinical trials of safety, effectiveness, and clinical significance will occur. Innovations in development are a spiral, applicator-tool, precalibrated closed sterile probe to measure the relation of tissue data to blood data, and meaningful display methods (human factors).

Title of Project: Fiberoptic Sensor for Continuous *In Vivo* Mg^{2+} Monitoring
Principal Investigator: Nathan Iyer, Ph.D.
Awardee Organization: International Biomedics, Inc.
1631 220th, Southeast
Bothell, WA 98021
Telephone Number: (206) 485-2200
Awardee Number: 1 R43 HD23436-01

The purpose of this proposal is to develop and qualify a continuous, miniature, atraumatic fiberoptic intravenous sensor and display system. The most common use of magnesium therapy is in obstetrics, where the infusion rate of $MgSO_4$ is regulated by clinical signs. The instantaneous regulation of $MgSO_4$ infusion will be safer and more effective with immediate feedback on the blood magnesium. A small, inexpensive, disposable, and continuously monitoring Mg^{2+} sensor would be cost effective, providing vital and immediate diagnostic and clinical feedback.

The specific aims of Phase I are to develop a Mg^{2+}-complexing dye system with suitable characteristics, to design a Mg^{2+} fiberoptic sensor and evaluate its performance, and to evaluate the practicality of instrumentation and calibration of the sensor. The longer term Phase II work will include finalizing the sensor design, calibration, and instrumentation and developing manufacturing methods for high-volume production.

Title of Project: Reliable Noninvasive Uterine-Activity Monitor
Principal Investigator: Page Read, Ph.D.
Awardee Organization: International Biomedics, Inc.
1631 220th Avenue, Southeast
Bothell, WA 98021
Telephone Number: (206) 485-2200
Awardee Number: 1 R43 HD23420-01

Current noninvasive monitoring of uterine activity in the pregnant woman is accomplished by tocotonometer devices which monitor continuously the hardness of the abdominal wall by measuring the force needed to push against the device. These electromechanical devices must be located over the fundus (top) of the uterus, fastened to the abdomen with a belt, and electronically connected to a fetal monitor. The devices are placement and artifact sensitive, bulky and uncomfortable for the patient, require frequent adjustment, and are delicate and expensive.

The objective of this project is to develop a soft, air-filled, pressurized "bladder" (air-cushion tocotonometer) that is held onto the abdomen with a belt. The bladder is compressed between the belt and the uterus, and the pressure increase is measured by any variety of standard pressure-measuring devices. It may be necessary to develop and include an electronic transducer interface to amplify the signals generated by the pressure changes. The performance is expected to be equivalent to standard tocotonometers. They will be comfortable, rugged, and inexpensive.

In Phase I, engineering models of the air-cushion tocotonometer will be demonstrated, their performance will be characterized, and clinical trials will be conducted to confirm in-house findings.

Title of Project: Neonatal-Sucking Instrument System
Principal Investigator: Reuben E. Kron, M.D.
Awardee Organization: KDI Technologies, Inc.
3508 Market Street
Philadelphia, PA 19104
Telephone Number: (215) 382-8324
Awardee Number: 1 R43 HD22652-01A1

The characteristics of nutritive sucking may serve as an indicator of the infant's general health and vitality, as well as indicate the presence of various sources of behavioral toxicity and central nervous system (CNS) dysfunction, such as may be caused by perinatal drug effects. The long-term goal of the proposed research is to develop and market a system that will facilitate the detection of abnormalities in nutritive sucking behavior (and recovery) within the nursery setting. It will also permit follow-up testing in the well-baby clinic and the home environment. Such a system will be useful in the screening for, and the diagnosis and treatment of, a variety of neonatal and infant disabilities and in the detection of heretofore unrecognized perinatal sources of CNS dysfunction.

The specific aims of Phase I are to establish the technical feasibility for developing a safe, inexpensive, and disposable diagnostic nipple device (along with its nondisposable computing component) and subsequently to begin evaluating the potential for such a diagnostic system to become a standard clinical method for screening the newborn for behavioral toxicity and CNS dysfunction and for following the recovery of the infant during the postnatal period. Ultimately, this system is envisioned as providing a routine clinical test to alert the neonatologist to the presence of behavioral abnormalities and to guide the clinician in performing more specific diagnostic procedures.

Title of Project: Special Education Shows Its Stripes—Evaluation of Bar Code Technology
Principal Investigator: Alan VanBiervliet, Ph.D.
Awardee Organization: Learning Express, Inc.
8029 Danwood
Little Rock, AR 72204
Telephone Number: (501) 565-8208
Awardee Number: 1 R43 HD22671-01

This research project is designed to evaluate the use of bar code technology for the education and habilitation of children with mental retardation and developmental disabilities. Three areas of study have been chosen to accomplish this aim: (1) the use of bar code technology to teach initial reading skills to children with mild and moderate levels of retardation; (2) the use of bar code technology as an augmentative aid for speech-impaired children; and (3) the use of bar code technology as a technique for teaching Braille to children with multiple handicaps. These studies will serve as the basis for further development of bar code technology for educational purposes and the development of validated educational materials for children with mental retardation and developmental disabilities.

The systems that will be studied are the Magic Wand Speaking Reader and Talking Track bar codes, developed by Texas Instruments. The Magic Wand consists of five basic components, including a fiberoptic reader, microprocessor, speech synthesizer, speaker, and power supply. The Talking Track bar codes contain coded instructions for producing words, sentences, sound effects, music, and instructions for a variety of educational tasks.

Title of Project: Microcomputer-Based System for Remediation of Dyslexia
Principal Investigator: Susan Dubicki
Awardee Organization: Optimum Resource, Inc.
Station Place
Norfolk, CT 06058
Telephone Number: (203) 542-5533
Awardee Number: 1 R43 HD23428-01

Optimum Resource, Inc.'s objective is the development of microcomputer software for the teaching of reading disabled students. These products will allow school systems to provide at

fective help to the large population of children who have not learned to read during the normal course of instruction.

This proposed research is designed to prove the feasibility of integrating, for the Apple microcomputer, software employing a letter-cluster methodology using color graphics, animation, sound, and computer-produced speech to teach remedial reading to dyslexic children 8 to 13 years of age. In addition, the system will test the latest in low-cost speech recognition equipment. The use of microcomputers will ease the workload on special education teachers and save schools millions of dollars, while enhancing the education of the students involved. Microcomputer-based education is ideally suited to the dyslexic student's need for repetition and reinforcement of basic reading skills.

This will be the only system available that teaches pronounceable and multiple-letter decoding units and trains children for speed in retrieving oral responses utilizing speech synthesis and recognition to interact with the child. Using the latest in modern technology and innovative teaching techniques, Optimum Resource, Inc. will produce a self-contained, teacher-independent system of remedial reading instruction.

Title of Project: Oral Delivery of a Sustained Estradiol Delivery System
Principal Investigator: Kerry S. Estes, Ph.D.
Awardee Organization: Pharmatec, Inc.
P.O. Box 730
Alachua, FL 32615
Telephone Number: (904) 462-1210
Awardee Number: 1 R43 HD23084-01

Studies are proposed to evaluate the feasibility of oral 17β-estradiol (E_2) administration using a novel redox system. This chemical delivery system (CDS) is based on an interconversion of a lipophilic dihydropyridine to a hydrophilic pyridinium salt, analogous to the NADH ⇌ NAD+ coenzyme system. It permits enhanced and sustained delivery of E_2 to the central nervous system by hydrolysis of a "locked-in," charged precursor. Sustained leutinizing hormone (LH) inhibition and increased brain drug concentrations were shown in rats after intravenous (i.v.) E_2-CDS treatment. No serum E_2 change was detected, indicating that E_2 was released centrally from charged E_2-CDS and decreased LH via central action and/or via portal vessel transit of E_2 to the pituitary.

Development of an oral formulation for E_2-CDS offers several advantages over currently available estrogen therapies including: (1) delivery of a naturally occurring gonadal steroid, (2) decreased peripheral estrogen activity, and (3) increased dosing intervals. The first study will establish bioavailability of the drug. The second study will compare LH-inhibiting activity of oral and i.v. E_2-CDS administration. The third study will examine the tissue distribution of drug and selected metabolites over time after oral E_2-CDS treatment.

Title of Project: Automated Chromosome Analysis
Principal Investigator: Thomas J. Golab
Awardee Organization: Potomac Medical Systems
P.O. Box 4212
Silver Spring, MD 20904
Telephone Number: (202) 625-2121
Awardee Number: 1 R43 HD22994-01

The long-term objective is to develop a preproduction prototype of the Extended Metachrome having capabilities for: (1) automating the karyotyping of hybrid cells, of fluorescence-stained chromosomes, and of prometaphase banding patterns; (2) automating analysis of fluorescence-stained interface cells, and of autoradiographs of previously scanned metaphases; and (3) including additional hardware features involving simultaneous imaging at high-

and low-power objectives, large-scale image storage and retrieval, and an automatic, glass slide-stack loader.

Such an Extended Metachrome instrument can greatly expand the applicability of automation to clinical genetic counseling, to genetic research, and to developments in genetic engineering. The current Metachrome instrument can increase the patient load of a technician by a factor of 5 to 10, thus making conventional chromosome analysis more widely available to the public; the Extended Metachrome promises to make feasible clinical applications of advanced genetic research results.

The present Phase I proposal is to develop the engineering data and hardware and software design leading to the fabrication of the Extended Metachrome. Commercial application of the final instrument should be widespread in genetic counseling laboratories and in genetic engineering research and development companies. In addition, the Extended Metachrome makes feasible for the first time large scale studies and developments, and clinical applications which heretofore would have been too tedious or expensive to perform.

Title of Project: Immunoassay for Human Progesterone Receptor
Principal Investigator: Naomi Eliezer, Ph.D.
Awardee Organization: Proteins International
1858 Star Batt Drive
Rochester, MI 48063
Telephone Number: (313) 852-1067
Awardee Number: 1 R43 HD22317-01A1

Progesterone receptor is one of a group of steroid hormone receptors that has been shown to have important regulatory effects in mammary and other target tissues. The qualitative and quantitative determination of progesterone receptor is useful in the therapeutic management of breast cancer. Currently, available assays for progesterone receptor have drawbacks that make them difficult to use in most clinical laboratories.

The major long-term goals of this proposal are the development of a sensitive, reliable, enzyme-linked immunoassay for progesterone receptor, the production of monoclonal antibodies capable of distinguishing among the various forms of the receptor, and the isolation of purified human progesterone receptor using an immunoaffinity resin prepared with one of the above monoclonal antibodies.

Title of Project: Isolation of Fetal Cells from Maternal Circulating Blood
Principal Investigator: Harold L. Sadoff, Ph.D.
Awardee Organization: Recomtex Corporation
4700 South Hagadorn Road, Suite 290
East Lansing, MI 48823
Telephone Number: (517) 332-1600
Awardee Number: 1 R43 HD23051-01

An increasing number of women delay pregnancy in favor of careers. Currently, 20 percent of all live births in the United States are to women over 30 years of age. The risk of an abnormal child due to chromosomal defects increases nonlinearly with age, 1 per 385 births for women age 30 and 1 per 61 births at age 39. Thus, it is understandable that women of advancing child-bearing age are highly interested in fetal chromosomal analysis.

This analysis, karyotyping, is currently done on tissue or cells obtained by chorionic villus sampling at 10 weeks or amniocentesis at 16 to 18 weeks gestation. Both procedures are surgically invasive and thus pose some risk to the fetus.

Recomtex Corporation proposes that fetal cells present in maternal circulating blood early in pregnancy can be utilized for karyotyping. Small blood samples were taken from the vein in

the arm of pregnant women at 7 to 12 weeks of gestation during each prospective mother's first visit to her obstetrician. The removed red and white blood cells and fetal cells were then isolated using appropriate immunological procedures. Human fetal cells are being cultured in preparation for karyotyping.

Title of Project: A Communication and Control System for the Mentally Retarded
Principal Investigator: Brian L. Scott, Ph.D.
Awardee Organization: Scott Instruments Corporation
1111 Willow Springs Drive
Denton, TX 76205
Telephone Number: (817) 387-9514
Awardee Number: 1 R43 HD23435-01

The topic of this proposal is the design of an environmental control system for the more than two million individuals in the United States whose physical and/or mental impairments are so severe that they are unable to function in their environment in a normal and effective manner. A two-year collaborative research effort between the bioengineering program at the National Headquarters of the Association for Retarded Citizens (ARC) and Scott Instruments has demonstrated that a woman with profound mental retardation, severe physical handicaps, and almost completely unintelligible vocalizations could learn to voice-activate a computer for the purposes of controlling various electrical devices in her environment. It was concluded from the study that speech recognition and activation of a computer by a person with severe multihandicaps is an appropriate use of technology that can be a positive intervention for the enhancement of life.

Although highly successful, this initial research effort uncovered a number of problems with the system. The current proposal addresses these problems through the use of current state-of-the-art speech-recognition technology, an object-oriented user interface for system setup, and an automated training procedure for the user.

Title of Project: Spectral Displays of Speech as an Aid to Reading
Principal Investigator: Rachel E. Stark-Seitz, Ph.D.
Awardee Organization: Stark and Associates
804 Maxalea Court
Baltimore, MD 21239
Telephone Number: (301) 377-9393
Awardee Number: 1 R43 HD22663-01

The proposed project is designed to test the effectiveness of real-time spectral displays of speech in teaching reading to first-grade language-impaired (LI) children. Young LI children are delayed in development of rapid-rate auditory processing and speech perception skills. They also have difficulty with phonics in reading. Spectral displays of speech may help them to segment speech into syllables and phonemes, and to match spoken words with written forms and phonemes with graphemes, thus facilitating early reading acquisition.

In Phase I, 12 LI children of 5½ to 7 years will be taught phonics with and without the aid of spectral displays. Their performance on tests of reading monosyllables and matching monosyllabic words with pictures will be compared before and after training, and under the two training conditions. Schematized spectrograms will also be generated, in color, using an IBM-compatible personal computer. In Phase II, amplitude displays will also be generated and displayed simultaneously with spectrographic displays and with printed graphemes. The system will be field tested and modified to increase effectiveness. The goal will be to make the system commercially available along with appropriate training materials.

Phase II Grants

Title of Project: Neonatal Nutrition and Resonance Ionization Spectroscopy
Principal Investigator: Larry J. Moore, Ph.D.
Awardee Organization: Atom Sciences, Inc.
114 Ridgeway Center
Oak Ridge, TN 37830
Telephone Number: (615) 483-1113
Awardee Number: 2 R44 HD21831-02

The feasibility of trace and ultratrace element determinations on microliter volumes of blood serum using resonance ionization spectroscopy (RIS) was established in Phase I. The development of instrumentation, methodology, and applications has the potential to further the understanding of the role of trace metals in premature infants. Trace element accumulation in the human fetus occurs during the last trimester of pregnancy, and premature birth interrupts this process at a critical time. Very little is known about trace element nutrition requirements in premature infants, or about the relationship of trace metals to observed dysfunctions, as the amount of blood available is <0.1 ml.

The specific aims of this proposal are to: (1) design, fabricate, and evaluate a commercial prototype instrument using RIS to determine ultramicro quantities of metals; (2) complete a study of trace metals in low-birth-weight (1,000 to 2,000 grams) preterm infants; and (3) develop a methodology for analytical services using ultramicro techniques and RIS. The technology developed will provide a commercial prototype RIS instrument for ultratrace element and isotope determinations, and the basis for service analyses for the neonatology and medical communities. The baseline study of trace metals will be the first performed with premature infants using sample sizes <0.1 ml.

Title of Project: Regulation of Biological Growth
Principal Investigator: E. Martin Spencer, M.D., Ph.D.
Awardee Organization: BioGrowth, Inc.
505 Ortega Street
San Francisco, CA 94122
Telephone Number: (415) 750-6054
Awardee Number: 2 R44 HD21323-02

The long-term objective of this project is to be able to regulate abnormal growth processes that are related to somatomedins. Since somatomedins are the major stimulators of bone formation, they offer real promise in the therapy of postmenopausal osteoporosis. They may also be used to stimulate bone formation around prosthetic joints. The stimulatory properties of somatomedins also may be important in hastening wound healing.

Title of Project: A Rapid, Simple Ovulation Test Requiring No Instruments
Principal Investigator: Deborah R. Siena, D.P.H.
Awardee Organization: Covalent Technology Corporation
3941 Research Park Drive, Box 1868
Ann Arbor, MI 48106
Telephone Number: (313) 769-5377
Awardee Number: 2 R44 HD20248-02

Covalent Technology Corporation (CTC) has a proprietary Visual Immunoassay (VIA) technology that is sensitive, rapid, easy to perform, and cost effective. It is widely acknowledged that a simple, rapid test for ovulation in women is needed. If an assay were available at a low cost, it could also be used in homes to predict time of ovulation and be a major advance for use with natural family planning methods. The economic feasibility, user friendliness, specificity and sensitivity, reagent stability, and speed of the VIA test should give it high commercial potential, especially in view of its easy applicability to an over-the-counter home-test situation.

In Phase II, CTC will further optimize the simple VIA test for the measurement of hLH in urine, perfom stability studies, develop and refine kit design, incorporate more user-friendly devices, and perform field testing. The long-term objectives are to develop a marketable kit and to obtain FDA approval for Phase III.

Title of Project: Identification of Infants at Risk for Mental Retardation
Principal Investigator: Patricia Ann Shepherd, Ph.D.
Awardee Organization: InfanTest Corporation
11000 Cedar Avenue, 4th Floor
Cleveland, OH 44106
Telephone Number: (216) 368-6476
Awardee Number: 2 R44 HD20731-02

Advances in medical care have allowed a greater number of neonates to survive, resulting in an increase in the number of infants at risk for later intellectual retardation. Happily, 80 to 90 percent of high-risk infants are intellectually normal later in life. Unfortunately, no valid screening device for differentiating infants who will later be intellectually normal from those who will be retarded is available.

The development of such a device would have several advantages. One is that parents of the majority of infants screened could be relieved of their anxiety and encouraged to treat their infants as intellectually normal. A second advantage is that identification of mental retardation during infancy may allow a fuller understanding of its causes. The ultimate goal of the proposed research is to make a valid screening device available to clinicians so that infants who will later be intellectually normal or mentally retarded may be identified during the first year of life.

The Fagan Test of Infant Intelligence is a valid screening device for the early identification of later mental retardation. Until recently, the Fagan Test existed solely as a research instrument. However, during Phase I, a prototype of a clinically useful screening device was developed. Its distribution, for an extensive clinical trial, is the main aim of the Phase II project. The commercial development of a valid screening device for the early detection of intellectual deficit promises to aid in diagnosing, understanding, and potentially, in preventing or alleviating mental retardation.

Title of Project: Cry Analysis as a Screening Test for SIDS
Principal Investigator: Howard L. Golub, M.D., Ph.D.
Awardee Organization: Pediatric Diagnostic Service, Inc.
221 Third Street
Cambridge, MA 02141
Telephone Number: (617) 661-0012
Awardee Number: 2 R44 HD20737-02

The goal of this proposal is to study the potential use of infant cry analysis in the identification of infants at risk for sudden infant death syndrome (SIDS). Pediatric Diagnostic Service (PDS), Inc. has used innovative signal-processing techniques to develop a prototype instrument capable of accurate and efficient acoustical analysis. During Phase I, the analysis system was refined and specifically adapted for Phase II studies. In addition, Phase I demonstrated the

feasibility of using existing relationships between PDS, Inc. and nationwide academic institutions as the basis for the Phase II collaborative study.

During Phase II of this project, PDS, Inc. will record and analyze the cries of a minimum of 30,000 newborn infants and determine the occurrence of SIDS during the first year of life. The study will include both low-risk (healthy term) and high-risk (premature) infants and test the hypothesis that acoustic properties of the cry will predict which infants will die of SIDS. Future research will utilize this information to direct further refinement and eventual commercialization of the cry analysis instrument.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Phase I Grants

Title of Project: Sustained-Release Fluoride Dentifrice
Principal Investigator: Elie S. Nuwayser, Ph.D.
Awardee Organization: BIOTEK, Inc.
21-C Olympia Avenue
Woburn, MA 01801
Telephone Number: (617) 938-0938
Awardee Number: 1 R43 DE08265-01

The overall objective of the 6-month project is to develop a sustained-release fluoride dentifrice formulation based on microcapsules with a duration of 12 to 24 hours. In Phase I, sodium fluoride microcapsules will be prepared and characterized for NaF content, geometry, and fluoride-release profile. A glycerin-based formulation will be developed for suspending the microcapsules, and the stability of the fluoride microcapsules in the formulation will be determined.

These studies will form the basis for more extensive preclinical testing of the formulation *in vitro* and in animals, which is planned for Phase II. The goals of Phase III are to secure an Investigational New Drug (IND) approval and proceed with clinical trials of the dentifrice in collaboration with a commercial organization.

The principal investigator was involved in two previous studies of microencapsulated sodium fluoride sponsored by NIDR. Sodium fluoride microcapsules, 38 to 300 microns, were recently prepared at BIOTEK, Inc. using a fluidized-bed process. Preliminary studies show fluoride release to be related to capsule geometry, thus confirming the predictions of release theory.

Studies of fluoride release in glycerin/water mixtures show that glycerin would be an excellent candidate for suspending and storing NaF microcapsules without leaching fluoride from the capsules. The final product will be a multicomponent toothpaste in which the glycerin microcapsule suspension is stored in parallel with a water-based paste. The two will be mixed immediately before use when the tube is squeezed to deliver the two pastes to the toothbrush.

Title of Project: High-Speed Turbine-Driven Handpiece with Air Bearings
Principal Investigator: Herbert Sixsmith, Ph.D.
Awardee Organization: Creare, Inc.
P.O. Box 71
Hanover, NH 03755
Telephone Number: (603) 643-3800
Awardee Number: 1 R43 DE07824-01

This Phase I program addresses the technological and economic feasibility of developing a high-speed dental handpiece using a radial inflow turbine operating in gas (air) bearings. Recent technological developments in the miniaturization of gas bearings and turbines indicate that faster speeds and smaller sizes are possible. These improvements offer several benefits, including reduced burr size, increased cutting speed, and improved handling.

The objectives of Phase I are to establish specifications and to perform preliminary design and costing. This effort will determine whether the proposed handpiece is feasible and what developments are required to demonstrate a working prototype. The long-term benefits of the production of the proposed handpiece include higher torque, less compressor power, lower noise, and potentially reduced drilling time.

Title of Project: Ultrahigh-Strength Dental Ceramics
Principal Investigator: Birol Sonuparlak, Ph.D.
Awardee Organization: Flow Research Company, Inc.
21414 68th Avenue South
Kent, WA 98032
Telephone Number: (206) 872-7080
Awardee Number: 1 R43 DE07953-01

The long-term objective of this project is to provide a superior dental ceramic prosthesis material and fabrication system to replace current gold- and porcelain-based technology. The aim of Phase I is to develop a new, reinforced glass-ceramic material with optical characteristics similar to natural teeth and with strength improved by more than a factor of two compared to the current most competitive dental ceramic. The new material should allow construction of all-ceramic bridges and crowns with a minimum thickness on occlusal surfaces of 0.75 mm or less, which is one-half of the current allowable minimum for ceramic crowns.

The proposal involves use of modern colloidal processing techniques and an understanding of composite design in brittle materials to identify several promising ultrahigh-strength systems to be experimentally evaluated. In Phase II, the material and fabrication system will be optimized and clinical testing initiated.

Title of Project: Sputtered Oxide for Dental Ceramic-Metal Bond
Principal Investigator: Susan J. Mroczkowski
Awardee Organization: Midwest Research Microscopy, Inc.
5510 West Florist Avenue
Milwaukee, WI 53218
Telephone Number: (414) 527-2260
Awardee Number: 1 R43 DE08248-01

The objective of the proposed research project is to investigate the use of a novel, gradient-composition, sputtered-oxide film for improving the bonding between metal and ceramic in porcelain-fused-to-metal dental restorations. The present process utilizes a discrete oxide layer formed by diffusion and an accumulation of oxide-forming elements from the bulk of the metal casting to the porcelain interface.

The alternate technique proposed here involves the magnetron sputter-deposition of a layer with a gradient oxygen composition that should have superior bonding to both the ceramic and metal components. The gradient will be achieved by slowly varying the gas composition during sputtering from argon to oxygen. This will result in a smooth compositional transition and may provide a reduction in the undesirable residual tensile stresses that occur at some porcelain-metal interfaces due to the difference in the thermal contraction coefficients. The use of this procedure may significantly improve the porcelain-metal bond strength, particularly with base metal casting alloys, and it should be less technique-sensitive than current dental laboratory procedures.

Title of Project: Antiplaque Proteins via Genetic Engineering
Principal Investigator: David I. Hirsh, Ph.D.
Awardee Organization: Synergen, Inc.
1885 33rd Street
Boulder, CO 80301
Telephone Number: (303) 938-6200
Awardee Number: 1 R43 DE07966-01

Synergen, Inc.'s proposed research will develop, through recombinant DNA methods, new agents to control dental plaque. These will consist of an enzymatic moiety of therapeutic value fused with an adhesive peptide that binds specifically and strongly to dental surfaces. The latter are termed adheson sequences, and the resulting technology, adheson technology. Using adheson technology to immobilize enzymes at the tooth surface will increase local concentrations of the enzymes and extend their residence times, thereby enhancing their therapeutic or prophylactic value.

The Phase I feasibility study will produce a set of prototype fusion proteins, each of which combines an adheson sequence with the enzyme beta-galactosidase. For each fusion, Synergen, Inc. will measure, *in vitro*, the binding to dental surfaces and the activity of the beta-galactosidase. By the end of Phase I, the sequences that bind most efficiently and support enzyme activity will be identified.

In Phase II, those sequences will be combined with therapeutic enzymes and these second-generation fusions evaluated *in vitro*. The most promising will be evaluated in animal models, then in clinical trials.

Adheson technology can be adapted to other dental technologies, including controlled-release delivery systems.

Phase II Grants

Title of Project: Nontoxic Pulpotomy Agent
Principal Investigator: Don M. Ranly, D.D.S., Ph.D.
Awardee Organization: Biomedical Development Corporation
1100 Northwest Loop 410, Suite 360
San Antonio, TX 78213-2254
Telephone Number: (512) 342-3898
Awardee Number: 2 R44 DE07261-02

This Phase II research evaluated the efficacy, stability, and toxicity of a glutaraldehyde-based pulpotomy agent. Using two *in vitro* assays, the shelf life of the preparation was determined for several storage conditions. The systemic distribution of glutaraldehyde from a pulpotomized rat molar was determined, and incremental doses of that basal body load were infused to evaluate toxicity in rats. Several biochemical tests and histopathologic examination revealed limited effects of the infused preparation, even at 4,000 times the amount distributed from a pulpotomy site. Minimal lethal-dose studies on rats demonstrated a significant tolerance for the preparation when administered orally. Pulpotomized teeth of dogs were treated with the preparation, and complete gross and histopathologic necropsy revealed no posttreatment conditions ascribable to the agent. Histology of pulpotomized rat molars treated with the preparation revealed a generally mild response. Further, application of the agent to smooth and abraded cheek mucosae of the rats resulted in no effect on smooth tissue and only a slight retardation of abraded tissue healing.

Biomedical Development Corporation concluded from these studies that the glutaraldehyde preparation is effective as a fixative, adequately stable for clinical requirements, and nontoxic under any reasonable clinical conditions.

Title of Project: Immunohistochemical Detection of Oral Dysplasia and Carcinoma
Principal Investigator: Raymond Ranken, Ph.D.
Awardee Organization: InTek Diagnostics, Inc.
1450 Rollins Road
Burlingame, CA 94010
Telephone Number: (415) 340-0530
Awardee Number: 2 R44 DE07539-02

There are no sensitive *in vitro* diagnostic tests for the detection of oral dysplasia or carcinoma. Although invasive epithelial malignancies are quite readily diagnosed, there are inconsistencies in the categorizing and diagnosis of what are generally termed dysplasias and other premalignant conditions. Transformation potential of what might appear to be normal or clear margins remains quite questionable. Immunodiagnosis may prove superior to the current method of subjective evaluation of cellular morphology, not only in terms of speed and sensitivity, but also in objectivity.

The development of a cocktail of highly associated squamous cell carcinoma monoclonal antibodies to be used as an immunohistochemical reagent will contribute to the effective diagnosis of oral disease.

The long-range goal of the research is to produce an immunohistochemical reagent that will (1) detect all stages of squamous cell carcinoma as well as all cells associated with the tumor mass; and (2) detect premalignant lesions.

Phase I monoclonals will be evaluated in a large-scale, double-blind clinical study in Phase II involving three centers.

Title of Project: New Controlled-Release Antibiotic Delivery System
Principal Investigator: Richard W. Baker, Ph.D.
Awardee Organization: Membrane Technology and Research, Inc.
1030 Hamilton Court
Menlo Park, CA 94025
Telephone Number: (415) 328-2228
Awardee Number: 2 R44 DE07022-02

This proposal covers Phase II of a program to develop a new method of treating periodontal disease. The approach is to develop a controlled-release antibiotic formulation that will release useful amounts of antibiotic for a period of at least 2 weeks when placed in the periodontal pocket by a dentist. In the Phase I program, the overall feasibility of the approach was demonstrated *in vitro*.

In Phase II, the formulation will be refined and demonstrated in a *Macaca fascicularis* model of adult periodontitis. Changes in the microflora of the periodontal pocket and bone-loss measurements will be used to quantify the ability of the formulation to control periodontal disease. The results, together with the appropriate supporting physical pharmaceutical data, will then be incorporated into an Investigational New Drug (IND) application. If the approach is technically successful, further development of the formulation into a commercially available product would be straightforward.

Title of Project: Interactive Videodiscs in Dental Practice
Principal Investigator: D. Joseph Clark, Ph.D.
Awardee Organization: VIDEODISCOVERY, Inc.
1321 Northlake Avenue
Seattle, WA 98103
Telephone Number: (206) 547-7981
Awardee Number: 2 R44 DE06778-02

In Phase II, VIDEODISCOVERY, Inc. proposes to further test the technical merit and feasibility of interactive videodiscs in preparing patients for major dental procedures. Phase I allowed the development and testing of the feasibility of an interactive videodisc for orthognathic surgery. The success of this prototype videodisc in enhancing patients' understanding and acceptance of orthognathic surgery suggests that such a tool may be equally valuable for patients undergoing conventional orthodontics, orthodontics in preparation for surgery, third molar extractions, osseointegrated implants, and periodontics.

The effectiveness of interactive videodiscs in improving patients' comprehension and expectations of the procedures they will undergo will be tested by comparing 20 patients who use the videodisc with 20 who receive traditional practitioner-based information for orthodontics and third molar extractions. Ten patients will be

tested with each of the other procedures and compared with 20 who do not view the disc. Pre- and post-procedure changes in comprehension and expectations will be examined for the two groups within each procedure.

If the interactive videodisc proves to be an effective patient preparation tool in these increasingly frequent dental procedures, it will enhance the level of patient satisfaction, acceptance, compliance, and use of such procedures. It will also aid the dental practitioner in providing appropriate and high-quality treatment.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Phase I Grants

Title of Project: Precision Shock-Wave Generator for Medical Treatment and Research
Principal Investigator: Nicholas Perrone, Ph.D.
Awardee Organization: Advanced Technology & Research, Inc.
14900 Sweitzer Lane
Laurel, MD 20707
Telephone Number: (301) 498-8200
Awardee Number: 1 R43 DK39934-01

This investigation intends to evaluate the capability of an established sector shock-tube method for application to lithotripsy. It could provide a quantitatively defined shock wave in terms of wave pressure, duration, energy, and spatial extent for improved patient treatment and use of shock waves in biological research. The only authorized shock-wave lithotripsy treatment system (Dornier) employs an elliptical focusing method that, because the focus is a mathematical singularity, is, in practice inherently unstable and not reproducible in a pressure amplitude and positional sense. All other proposed systems have similar limitations.

The sector shock-wave method, because it is quantitatively predictable, controllable, and reproducible, could lead to lithotripsy treatment that is faster, safer, less damaging, and easily adaptable to individual patient and various disease requirements.

The research effort includes design and fabrication of a conical sector shock tube that will be used to shock impact-simulated and actual stones while transient pressure measurements are made. Hydrodynamics code calculations will assist experimental design and correlation of results. Phase II studies with animals and humans will be based on these results. Commercially, this could provide an advanced third-generation lithotripsy system, a unique quantitative biological research tool, and a retrofit shock-wave source to upgrade existing lithotripsy systems.

Title of Project: Indwelling Fistula Access Device (IFAD) for Hemodialysis
Principal Investigator: Stephen R. Ash, M.D.
Awardee Organization: Ash Medical Systems, Inc.
2701-B Kent Avenue
West Lafayette, IN 47906
Telephone Number: (317) 463-9540
Awardee Number: 1 R43 DK39280-01

Effective hemodialysis requires a blood flow of 250 to 300 ml/minute. The usual method for obtaining this blood is to place two large needles into a fistula (arterialized vein) or a graft (PTFE conduit between artery and vein). Both needles are removed at the end of each treatment.

The objective of this proposal is to further develop an indwelling fistula access device (IFAD) that can be inserted into a fistula or graft, left in place for several weeks or months, and used for numerous hemodialysis treatments. Blood access would then be rapid, painless, and bloodless.

The IFAD will be constructed from two sizes of stainless-steel needle stock. A 20-gauge needle with point is welded into the front of a 17-gauge needle, near a side hole in the larger needle (for blood removal or return). The small needle is inserted first into the fistula or graft, and rotation brings this needle through the skin, where a cap is placed to close it and to stabilize the device. The rotation also brings the side hole of the 17-gauge needle into the fistula. Animal tests with a similar 16-gauge device have shown that the IFAD can be left in place for up to 4 months without clotting, phlebitis, or infection. This impressive biocompatibility is due to immobilization of the device and to avoiding the trauma of a needle point within the fistula.

During this project, in vitro tests will determine the hydraulic resistance of the IFAD. Animal tests will determine the longevity, biocompatibility, resistance to infection, and ease of removal of the device. If these tests are successful, an Investigational Device Exemption (IDE) proposal will be prepared for submission to the Food and Drug Administration for human testing of the device.

Title of Project: A New Sorbent System for Hemodialysis Treatment
Principal Investigator: Stephen R. Ash, M.D.
Awardee Organization: Ash Medical Systems, Inc.
2701-B Kent Avenue
West Lafayette, IN 47906
Telephone Number: (317) 463-9540
Awardee Number: 1 R43 DK39307-01

Ash Medical Systems, Inc. has developed a new sorbent-based, single-access hemodialysis machine that is safe, simple, and portable. The BioLogic-HD currently uses a plate dialyzer to actively pump blood while dialyzing the blood and a Redy HiSorb column to regenerate dialysate. Previous research has proven that a thick sorbent suspension can flow through the screen supports of the plate dialyzer, replacing the Redy column. A sorbent suspension in the dialysate can produce higher clearances of uremic toxins and can use sorbents with light density and small particle size, which are difficult to put into columns, such as zeolites.

The current proposal is to further develop a sorbent suspension that will effectively remove uremic toxins, release appropriate substances, and minimize release of potentially harmful substances. This sorbent suspension will include powdered charcoal and microcapsules, which include calcium-sodium-loaded zeolites and urease. *In vitro* tests will demonstrate the safety and efficacy of the sorbent suspension. If these tests are positive, an Investigational Device Exemption (IDE) proposal will be submitted to the Food and Drug Administration to allow clinical trials of the sorbent suspension in the BioLogic-HD system.

Title of Project: Trace Chromium in Diabetes Using Resonance Ionization
Principal Investigator: Larry J. Moore, Ph.D.
Awardee Organization: Atom Sciences, Inc.
114 Ridgeway Center
Oak Ridge, TN 37830
Telephone Number: (615) 483-1113
Awardee Number: 1 R43 DK39921-01

Trace element nutriture is increasingly acknowledged as a key aspect of growth, development, and health. Trace chromium may be related to regulation of insulin action, restoration of impaired glucose tolerance, and the causal origin of a substantial portion of diabetes cases. However, trace chromium research has been greatly handicapped by low chromium levels in biological samples and by the general unavailability of methods with sensitivity beyond atomic absorption spectrophotometry. Further hindrance has resulted from unavailability of physiologically relevant tissue to determine chromium status or to evaluate response to intervention.

Recent developments in resonance ionization spectroscopy may lead to absolute chromium sensitivities of a few thousand atoms, with attendant isotope dilution reliability, simplified sample preparation, multielement analysis potential, and stable isotope tracer capability.

Feasibility will be demonstrated with a pilot study of chromium in skin biopsies from men with psoriasis who have abnormal glucose tolerance with increased insulin/glucose ratios. Successful results from this project will allow a greatly expanded study in Phase II of the role of chromium deficiency in glucose intolerance and diabetes. Commercial applications include the application of methodology for screening the prediabetic condition and the dissemination of instrumentation for ultratrace chromium determinations.

Title of Project: Noninvasive Monitoring of Kidneys Awaiting Transplant
Principal Investigator: Clyde H. Barlow, Ph.D.
Awardee Organization: Barlow Scientific
6307 Tamoshan Drive, Northwest
Olympia, WA 98502
Telephone Number: (206) 866-1244
Awardee Number: 1 R43 DK37734-01

The long-term goal of this research is to construct and evaluate a noninvasive device that will assess the functional integrity of hypothermic perfused kidneys prior to transplant. The device is based on measurements of changes in mitochondrial electron-transport protein-oxidation states in the kidney cortex. These changes can be measured spectrophotometrically and will be imaged at the surface of the hypothermic perfused kidney with the device to be developed in this proposal.

In Phase I, rat kidneys will be perfused under hypothermic conditions and reflectance spectra of the kidney cortex recorded at incremental perfusion pressures. Similar spectra will also be recorded for chemically uncoupled kidneys and for kidneys that have been subjected to warm ischemia. Reduction in cytochromes c and aa_3 will be correlated with renal perfusion flow, oxygen consumption, and physiologic measures of renal function. An imaging reflectance spectrometer will be constructed. Using wavelengths and conditions established in the scanning studies, monochromatic images of the kidney cortex will be collected and processed to produce a false color image of the kidney that depicts areas of mitochondrial uncoupling and ischemia.

Phase II studies will establish correlations between the cortical mitochondria functional state under hypothermic perfusion and time for recovery of renal function following transplant and viability of the transplanted kidney.

Title of Project: Procedure to Produce High-Specific-Activity ^{32}P-IP_3
Principal Investigator: David L. Clapper, Ph.D.
Awardee Organization: Bio-Metric Systems, Inc.
9932 West Seventy-Fourth Street
Eden Prairie, MN 55344
Telephone Number: (612) 829-2700
Awardee Number: 1 R43 DK39266-01

Inositol trisphosphate (IP_3) has recently been shown to stimulate Ca^{2+} release in a variety of cell types and, therefore, mediates such processes as muscle contraction, hormone secretion, and liver metabolism. In order to investigate the mechanism of IP_3 action and to develop therapeutic drugs that act by duplicating or inhibiting IP_3 action, one essential line of research is to study IP_3 binding to its receptor. Such receptor-binding studies require radioactively labeled IP_3 with a high specific activity. The method proposed here would produce ^{32}P-IP_3 with a specific activity greater than 10-fold higher than what is now available commercially or reported in scientific literature. The proposed protocol will use a readily available enzyme and ^{32}P-ATP to label the precursor of IP_3; therefore, purified phosphatidylinositol phosphate will be labeled to produce ^{32}P-phosphatidylinositol bisphosphate (^{32}P-PIP_2). ^{32}P-PIP_2 will then be hydrolyzed to produce ^{32}P-IP_3, which will be purified. Its specific activity will then be determined.

The longer-term (Phase II) objectives are to optimize the procedure and to verify the utility of ^{32}P-IP_3 in receptor studies. ^{32}P-IP_3 is expected to be utilized both in basic research and in evaluating potential therapeutic drugs that act as IP_3 agonists or antagonists.

Title of Project: A Novel Cytochemical Bioassay for Parathyroid Hormone
Principal Investigator: Carol Varanelli
Awardee Organization: Cambridge Medical Diagnostics, Inc.
575 Middlesex Turnpike
Billerica, MA 01865
Telephone Number: (617) 667-2161
Awardee Number: 1 R43 DK37738-01

Radioimmunoassays (RIAs) represent the standard methodology for the measurement of parathyroid hormone (PTH). However, there are a number of limitations associated with the measurement of PTH by this technique. Most immunoassys are insensitive and, therefore, cannot detect circulating levels of hormone in normal subjects. Consequently, RIAs cannot distinguish normal from hypoparathyroid levels of PTH. Most RIAs are heterologous systems that often utilize bovine PTH as the radioligand and antisera raised against bovine PTH to measure human PTH.

A major factor complicating PTH-RIA techniques is the presence of multiple forms of circulating hormone. A preponderance of midregion/carboxy-terminal hormone fragments exist in the circulation, but these forms of the peptide are without biological activity and have prolonged half-lives compared to biologically active intact PTH (1-84). The heterogeneity of the hormone contributes to the high noise-to-signal ratio encountered in most PTH-RIAs.

The cytochemical bioassay (CBA) for PTH circumvents the problems associated with RIA and represents the most sensitive method currently available for measuring this hormone, but this assay has not gained widespread use because it is labor intensive, has limited sample throughput, and requires expensive instrumentation. Preliminary data suggest that this sensitive assay system can be modified, creating the opportunity to develop a powerful diagnostic assay for commercial purposes that is free of the limitations of the original CBA.

Title of Project: Design and Evaluation of a Compound Tracheal Prosthesis
Principal Investigator: Richard E. Hoffer, D.V.M.
Awardee Organization: Deseret Research Company, Inc.
UBTL, Inc. Division
520 Wakara Way
Salt Lake City, UT 84108
Telephone Number: (801) 583-3600
Awardee Number: 1 R43 DK39271-01

The proposed study is designed to develop and evaluate a method of replacing the trachea with a compound prosthesis that will be epithelized at the time of implantation by tissue culture of buccal mucosa or a free graft of tracheal mucosa. Healing of the cervical trachea to two types of prostheses will be evaluated in dogs. Both types will have a rigid polyethylene outer layer and a middle layer of atelocollagen. The inner layer, or Type 1 prosthesis, will consist of buccal mucosal tissue cultured onto the collagen layer. The Type 2 prosthesis will have a free graft of tracheal mucosa. The prostheses will be evaluated at various postimplantation times of up to 60 days. Evaluation of the surgical sites for grafted and cultured mucosal healing, proliferation, connective tissue growth, scarring, infection, and rejection will be performed by gross examination and histopathological methods.

Title of Project: Multiparameter Metabolic Pattern Infection Diagnosis
Principal Investigator: Wayne R. Matson, Ph.D.
Awardee Organization: ESA, Inc.
45 Wiggins Avenue
Bedford, MA 01730
Telephone Number: (617) 275-0100
Awardee Number: 1 R43 DK38805-01

Continuous ambulatory peritoneal dialysis (CAPD) is now recognized as a feasible alternative for hemodialysis in end-stage renal failure. The rapid and potentially lethal development of peritonitis is a major limitation and concern for the CAPD physician and patient.

Current conventional techniques for culturing, detecting, and classifying infection in CAPD are not fully adequate to treat peritonitis. The recent development of computerized, multiple electrochemical sensor chromatography technology (n-ELC) offers a route to a rapid instrumental diagnosis of CAPD infection through the detection of unique, small-molecule pathogen metabolites. Current n-ELC technology takes 60 minutes to separate and can detect approximately 250 compounds in peritoneal dialysate at femtogram sensitivities. Preliminary work has indicated that 6 to 8 of these are associated with infection.

The proposed work involves verification and identification of unique markers and the development of rapid n-ELC testing protocols to open a market for the current n-ELC research equipment in infectious diseases.

Title of Project: Glucose Sensors with Improved Stability
Principal Investigator: Srinivasam Sarangapani, Ph.D.
Awardee Organization: Giner, Inc.
14 Spring Street
Waltham, MA 02154
Telephone Number: (617) 899-7270
Awardee Number: 1 R43 DK39923-01

The development of an implantable glucose sensor could provide closer control of glucose levels in diabetics than is now possible. Glucose sensor research, using a catalytic metal sensor based on platinum, is currently being performed by Giner, Inc. Considerable progress has been made so far in improving the sensitivity and short-term stability of the sensor; improvements in selectivity toward glucose in the presence of coreactants are under way.

The purpose of the proposed research is to improve the longevity of electrocatalytic glucose sensors based on platinum. Maintenance of a sensor response at a constant level over an extended period of time is desirable, because it avoids the need for frequent calibration. Preliminary studies with specially formulated polymer-bonded, platinum black electrodes show improved stability. The proposed work attempts to develop this concept further and prove its feasibility through rigorous testing and analysis.

Title of Project: Modification of Carbon for Wearable Artificial Kidneys
Principal Investigator: Jose D. Giner, Ph.D.
Awardee Organization: Giner, Inc.
14 Spring Street
Waltham, MA 02254-9147
Telephone Number: (617) 899-7270
Awardee Number: 1 R43 DK39288-01

The long-term objective of the proposed work is to modify carbon cartridges for efficient removal of blood toxins. Carbon adsorption is employed for the removal of strongly adsorbable toxins in some artificial kidney systems as well as in most artificial liver configurations. In the regenerative artificial kidney application, a carbon bed with about 250 grams of activated carbon is used to adsorb the strongly adsorbable species that accumulate between dialysis sessions.

The specific aim of Phase I is to demonstrate the feasibility of reliable modification of a carbon bed. The model species to be investigated will be creatinine, uric acid and vitamin B_{12}, and urea.

With the successful completion of these modification methods, Giner, Inc. will prepare a preliminary conceptual design of a regeneration system and a procedure for two applications: (1) carbon beds used to adsorb uric acid, creatinine middle molecules, etc., in regenerative, closed-loop artificial kidneys, such as the electrochemically regenerative artificial kidney being developed by Giner, Inc. and the Redy System, and (2) an artificial kidney based on the adsorption of urea using carbon.

Title of Project: An Efficient Method for Generating Full-Length cDNA
Principal Investigator: Paul Gold, Ph.D.
Awardee Organization: Gold Biotechnology, Inc.
5050 Oakland Avenue
St. Louis, MO 63110
Telephone Number: (314) 534-7609
Awardee Number: 1 R43 DK39277-01

Gold Biotechnology, Inc. is studying a new method for generating full-length cDNA. This method should be simple and efficient and thus allow cloning of both rare and abundant mRNA. This method improves upon other procedures in the following ways: (1) no S1 nuclease is required for cloning cDNA into the vector, and (2) tailing of cDNA is unnecessary for both insertion of the cDNA into the vector and circularization of cDNA vector hybrid.

The synthesis of full-length cDNA can be exploited to produce important commercial products. These include materials such as growth factors, hormones, and immunoregulatory molecules. In addition to direct commercial products, therapeutic use of full-length cDNAs may become important as antisense mRNA technologies are improved. This project will demonstrate the superiority of the proposed cDNA method using globin mRNA, a homogeneous template.

Title of Project: Automatic High-Speed White-Cell Differential Counting
Principal Investigator: Harvey L. Kasdan, Ph.D.
Awardee Organization: International Remote Imaging Systems, Inc.
9825 De Soto Avenue
Chatsworth, CA 91311
Telephone Number: (818) 709-1244
Awardee Number: 1 R43 DK39082-01

The purpose of this project is to demonstrate the feasibility of a moderate-cost, high-performance instrument utilizing metachromatic staining and very high-speed image processing for automatic differentiation, identification, and enumeration of human blood leukocytes.

Such an instrument will provide significant economic benefit in the clinical laboratory and substantially improve routine test precision. Commercial development will be based on adding this capability to an existing commercial imaging flow cytometer and a soon-to-be introduced high-speed microscope cytometer.

This study will utilize the high-speed microscope cytometer to collect and process leukocyte image data in order to extract features for leukocyte differentiation. Recognition algorithms will be developed using off-line computing.

Title of Project: Improved Long-Bone Measuring Device
Principal Investigator: Kusum K. Mainigi, Ph.D.
Awardee Organization: Intersciences, Inc.
3508 Science Center, Suite 212
Philadelphia, PA 19104
Telephone Number: (215) 662-0700
Awardee Number: 1 R43 DK39500-01

The aim of this project is to develop and test an improved, cost-effective, dual-purpose long-bone measuring instrument as an integral member of a family of computer-assisted anthropometric devices. The proposed instrument will permit highly accurate measurement of small increments in the length of lower arm and lower leg bones. Prototype instruments will be constructed and bench tested in Intersciences, Inc.'s engineering facilities. Design evaluations and reliability tests will be performed on these instruments, using growth-hormone-treated and normal subjects who will be observed at Hahnemann University Hospital.

The proposed instrument represents a radical departure from all previous long-bone measuring devices in: (1) offering in a single instrument the capability for accurate measurement of both knee height and ulnar length; (2) providing a more attractive alternative to the expensive, cumbersome, and difficult-to-use devices currently available; and (3) being designed and eventually marketed as an integral member of a family of computer-assisted anthropometric instruments.

Title of Project: Exoscope System for Laser-Welding Bowel Anastomoses
Principal Investigator: Jude S. Sauer, M.D.
Awardee Organization: Lasersurge, Inc.
P.O. Box 20333
Rochester, NY 14602
Telephone Number: (716) 461-1689
Awardee Number: 1 R43 DK39287-01

The use of laser energy to weld tissue and to create sutureless anastomoses has great potential. Many laser-welded tissues can withstand physiologic stress without weakening and heal with good restoration of function. Investigators have welded bowel in rabbits and rats. Lasersurge, Inc. is developing a unique, patented, fiberoptic system that provides for the automated application of laser energy to intracorporal tissue sites for the production of sutureless anastomoses of hollow organs. The purpose of this proposal is to facilitate the further development and testing of the exoscope system for the production of bowel end-to-end anastomoses. Using Nd:YAG laser energy and rabbits, the feasibility, strength, and efficiency of small intestinal, exoscope-welded anastomoses (N=70) will be compared to standard sutured anastomoses (N=35). Using dog colon, 18 welded anastomoses will be compared to 6 sutured and 6 stapled anastomoses. Potential advantages of exoscope system laser-welding range from minimal inflammation with fewer strictures and adhesions to automated precision with diminished surgical time. Once fully developed and commercialized, Lasersurge, Inc.'s proprietary bowel exoscope system technology could gain worldwide acceptance as a human surgical technique.

Title of Project: Chemiluminescence Immunoassay for Insulin
Principal Investigator: Russell C. Hart, Ph.D.
Awardee Organization: London Diagnostics, Inc.
10300 Valley View Road, Suite 107
Eden Prairie, MN 55344
Telephone Number: (612) 941-3812
Awardee Number: 1 R43 DK38797-01

The aim of this project is to demonstrate the feasibility of an immunoassay for insulin, using acridinium esters as a chemiluminescent label. This will lead to a technique for the detection of polypeptide hormones that is faster and more sensitive, and removes the need for ^{125}I-labeled peptides or antibodies.

The project will explore both traditional immunoassays in which the insulin molecule is labeled and "sandwich"-type assays in which insulin antibodies are used. In the first case, labeled insulin will be purified by high-performance liquid chromatography (HPLC) and directly substituted as the tracer in a radioimmunoassay (RIA) procedure. For the immunometric assay, antibodies to insulin will be labeled and purified by gel filtration chromatography.

The labeled peptide and antibody will be compared for stability against a commercially available RIA using ^{125}I-labeled insulin. The assay will serve as a model for other peptide hormone assays that require high sensitivity and stable reagents. The project will involve limited assay development, comparison with a commercial RIA, and a limited trial with plasma samples.

The multimillion-dollar hormone RIA market might increase if more stable, safer, cheaper, and simpler assays were available using chemiluminescence detection techniques.

Title of Project: Improved Urethral Profilometry Measurement
Principal Investigator: Richard H. Eckhouse, Jr., Ph.D.
Awardee Organization: MOCO, Inc.
91 Surfside Road
P.O. Box A
Scituate, MA 02055
Telephone Number: (617) 545-2040
Awardee Number: 1 R43 DK39939-01

The objective of this research is to develop a method for profiling urethral pressure using a nonmoving transducer that provides a dynamic presentation of the urethral pressure over its entire length. The approach is based on a physical property called magnetostriction that takes advantage of the volume changes in magnetic materials.

The specific aims of the project are to develop a laboratory prototype for magnetostrictive measurement of urethral pressure profiles (Phase I) and to make *in vivo* measurements with human subjects (Phase II). The methodology for Phase I involves constructing a working prototype device for laboratory experimentation and making *in vitro* measurements with this prototype in an artificial urethra under simulated human conditions.

The innovative aspects of the research lie in the novel application of the magnetostrictive property and in the realization of an instrument that will measure urethral pressure without introducing the artifacts that traditional measuring techniques produce due to canal irritation and transducer twisting and mispositioning.

Title of Project: Development of a Carrier Screening Test for Gaucher Disease
Principal Investigator: William D. Huse, M.D., Ph.D.
Awardee Organization: Stratagene Cloning Systems
11099 North Torrey Pines Road
La Jolla, CA 92037
Telephone Number: (619) 535-5431
Awardee Number: 1 R43 DK39275-01

Gaucher disease affects 20,000 individuals in the United States. Gene frequency for this disease is particularly high in the Ashkenazic Jewish population, in which 1 out of 20 individuals is a carrier. It is more common than Tay-Sachs disease, for which a successful carrier screening program exists. There is currently no heterozygote carrier test that is suitable for a Gaucher disease screening program.

Stratagene Cloning Systems proposes to determine the common gene mutations responsible for type I Gaucher disease. It plans to accomplish this project using a new gene-cloning and gene-sequencing technology. Once the common alleles have been sequenced, a panel of mutant-specific oligonucleotides will be synthesized for screening purposes. The objective is to develop a test, analogous to the Tay-Sachs carrier screening test, for Gaucher disease.

Title of Project: Cloning, Sequencing, and Expression of Human BSA Lipase cDNA
Principal Investigator: John M. Maraganore, Ph.D.
Awardee Organization: ZymoGenetics, Inc.
2121 North 35th Street
Seattle, WA 98103
Telephone Number: (206) 932-4036
Awardee Number: 1 R43 DK39294-01

Bile salt-activated lipase (BSAL) is found in the milk of a limited number of mammals: humans, gorillas, dogs, and cats. The enzyme plays an important role in the infant diet in the digestion of lipids, causing a striking quantitative difference between breast-fed and formula-fed infants in weight gain. In this regard, it is important to note that BSAL is absent in bovine milk.

In Phase I, ZymoGenetics, Inc. plans to clone, sequence, and express the cDNA for human BSAL. This will provide a framework for Phase II research, wherein recombinant human BSAL will be produced in large quantities for supplementation in infant formulas. Expression of the human BSAL cDNA will be achieved by cloning into an expression vector suitable for production at high levels in *Saccharomyces cerevisiae*. Levels of expression will be ascertained by ELISA and direct measurements of enzymatic activity. The recombinant protein will be purified and characterized for its physical and chemical similarity to the purified human milk enzyme.

Phase II Grants

Title of Project: Implantable Hollow Fiber Glucose Sensor
Principal Investigator: Elsa Janle-Swain, Ph.D.
Awardee Organization: Ash Medical Systems, Inc.
2701-B Kent Avenue
West Lafayette, IN 47906
Telephone Number: (317) 463-9540
Awardee Number: 2 R44 DK35550-02

Ash Medical Systems, Inc. proposes to develop two closely related devices to improve home and hospital monitoring of glucose for diabetics. The common element of both devices is a subcutaneously implanted fiber. Negative pressure is applied to this fiber to withdraw tissue fluid. In the ambulatory model, fluid will be collected and analyzed using one of the currently available blood glucose strips and a reflectance meter. Because painful finger pricks are eliminated, glucose values can be obtained as often as is necessary to maintain good control. In the hospital model, fluid will be analyzed directly by an optical system. This hospital model will allow constant monitoring of blood glucose without any delay between drawing the sample and obtaining the results. The aims of this project are to build and test these glucose-sensing devices *in vitro* and *in vivo* in dogs.

These devices will have significant commercial potential. The potential market for the ambulatory device is insulin-dependent diabetics. The hospital model provides an inexpensive system for constant monitoring. Other instruments that monitor constantly are very expensive and are, therefore, currently available only in the largest hospitals. In addition, the proposed system has the potential to be adapted for constant monitoring of many other tissue constituents, including drug levels.

Title of Project: Synthesis of High-Molecular-Weight Iron Chelators
Principal Investigator: Bo Erik Hedlund, Ph.D.
Awardee Organization: Biomedical Frontiers, Inc.
1095 10th Avenue, Southeast
Minneapolis, MN 55414
Telephone Number: (612) 378-0228
Awardee Number: 2 R44 DK37207-02

In the past 40 years, biochemical researchers have investigated the deleterious effects of free or reactive iron, and recent experiments have examined its significance in biology and medicine. The results suggest that iron, in conjunction with oxygen radicals, plays an important role in a number of different clinical situations, including myocardial infarct, shock, stroke, surgery, and trauma. These data imply that the chelation or inactivation of iron may have considerable therapeutic potential.

The only iron chelator currently approved for clinical use, deferrioxamine, has therapeutic limitations because of its short circulatory half-life and toxicity. An assortment of modified iron chelators has been developed by attaching deferrioxamine to either polysaccharide or peptide polymers, thereby increasing its molecular weight. These high-molecular-weight chelators manifest decreased toxicity and increased circulatory retention times, and they may have significant therapeutic potential.

The goal of this Phase II proposal is to advance the development of a family of therapeutics that can be utilized when iron-dependent pathophysiology is suspected in the etiology of a clinical condition. The iron chelation efficiency of these novel compounds will be assessed, and their physical and biochemical properties will be characterized. The production of these chelators will be increased, and their therapeutic efficacy will be assessed in animal models in several clinical conditions.

Title of Project: Laser Fragmentation of Biliary Stones
Principal Investigator: James C. Hsia, Ph.D.
Awardee Organization: Candela Laser Corporation
530 Boston Post Road
Wayland, MA 01778-1883
Telephone Number: (617) 358-7637
Awardee Number: 2 R44 DK37754-02

Stone disease of the gastrointestinal tract affects over 16 million people in the United States. Approximately 1 million new cases of cholelithiasis develop each year, and surgical intervention was required in 554,000 procedures in 1984. The average length of hospitalization for these patients is between 9 and 16 days.

Candela Laser Corporation performed *in vitro* and animal studies in Phase I to establish optimum laser parameters for safe and effective fragmentation of biliary stones. In Phase II, more effective delivery systems will be developed. If successful, this research will lead to commercialization of a clinical system.

Title of Project: Improved Skinfold Caliper Systems
Principal Investigator: Kusum K. Mainigi, Ph.D.
Awardee Organization: Intersciences Development Associates, Inc.
3508 Market Street, Suite 212
Philadelphia, PA 19104
Telephone Number: (215) 662-0700
Awardee Number: 2 R44 DK36236-02A1

The long-range goals of this project are to develop a complete skinfold caliper system for the accurate assessment of total and segmental body fat in young and adolescent populations. Features of the prototype developed in Phase I include digital display, online data storage, and a semiautomated, interactive control system designed to facilitate ease of use and to minimize observer error. Automated controls will compensate for differences in skinfold compressibility attributable to hydration, size of measurement, and individual tissue variations.

The Phase II clinical research goal will be to determine the equations necessary to predict the duration of skinfold compressibility and to refine and modify the Phase I instrument for marketing. These equations will provide the basis for an automation feature of critical importance, i.e., accurate and reliable skinfold reading with a much briefer standard duration of skin compression. These various features define a useful, competitively priced, and widely marketable tool for monitoring a clinically important aspect of various groups such as the obese and athletes, as well as individuals with various health disorders. A strong market for the fully developed system is anticipated in a wide variety of medical and research settings. Phase II engineering refinements will reduce the cost of the system.

Title of Project: Interactive Self-Reported Diet Assessment
Principal Investigator: Teresita B. Hernandez, Ph.D.
Awardee Organization: JWK International Corporation
7617 Little River Turnpike
Annandale, VA 22003
Telephone Number: (703) 750-0500
Awardee Number: 2 R44 DK35548-02A2

The primary objective of this Phase II project is to fully develop and evaluate an interactive microcomputer software for a self-reported dietary assessment instrument. The framework for dietary assessment is a stepwise food group selection and quantification of the respondent's usual (or time-referenced) intake of specific foods within the groups selected. The proposed project capitalizes on the technological advances in microcomputers with graphics capability and the demonstrated increase in respondent interest and ability to interact personally with computer queries.

The commercial product is a software package that will be developed for the Apple Macintosh computer. The program is respondent directed, using the "mouse" as an input device, and is designed to have responses automatically coded and stored for research purposes. It contains several improvements over current methods. Queries, including quantity estimations, are presented to respondents in a uniform way. Because respondents interact with personal computers directly, interviewer variability and possible bias are eliminated. Coding and quantity conversions are computer generated, thereby eliminating a tedious, time-consuming process and coding errors. Frames of questions are modular and can be presented to the respondent in a selective fashion, depending on study needs and respondent's attention span.

A full evaluation will be conducted to assess the effectiveness of the system in generating quantifiable dietary intake, response time, and respondent acceptability.

Title of Project: Development of an Immunospecific Assay for Hgb A_{1c}
Principal Investigator: Jin Po (James) Lee, Ph.D.
Awardee Organization: Leeco Diagnostics, Inc.
21705 Evergreen Road
Southfield, MI 48075
Telephone Number: (313) 353-2620
Awardee Number: 2 R44 DK33369-02

The primary objective of this effort is to improve existing methodologies for assay of hemoglobin A_{1c} in human blood by utilizing monoclonal antibody technology in the development of an immunospecific assay. In recent literature, the clinical usefulness of the assay as an objective measure of long-term carbohydrate control of diabetic patients has been favorably discussed. The assay can also be used in monitoring and encouragement of patient compliance, in reversal of certain pathological sequelae of diabetes, in lowered perinatal mortality and morbidity to pregnant diabetics, in minimization of hypoglycemic reactions, and as an adjunctive test of high specificity in the diagnosis of diabetes mellitus.

Phase II efforts consist of completing the characterization of the monoclonal antibodies specific for hemoglobin A_{1c} and hemoglobin A_0 produced under Phase I funding; production of additional monoclonal antibodies, seeking those with optimal affinities; incorporation of the antibodies in one of three alternative approaches; and evaluation of the utility and performance of the optimized assay in different clinical conditions. The uniqueness of the proposed highly sensitive and specific enzyme immunoassay derives from the anticipated improvements over existing methodologies, and the high likelihood of commercial success is assured by a large existing market, which will grow with increasing awareness and a better test.

Title of Project: Development of Fiberoptic Sodium and Potassium Sensors
Principal Investigator: Roger A. Wolthuis, Ph.D.
Awardee Organization: METRICOR, Inc.
18800 142nd Avenue, Northeast, Suite 3
Woodinville, WA 98072
Telephone Number: (206) 483-5577
Awardee Number: 9 R44 DK39268-02

METRICOR, Inc. proposes the continued development of fiberoptic sodium and potassium sensors and systems. Sensor development will focus on improving the sensitivity and selectivity of respective active chemistries, improving the chemical and optical properties of the matrix substrate, and improving the method of attaching active chemistries to the matrix substrate. System development will focus on the design and testing of dedicated, second-generation hardware and software that support the respective sensor technologies. Completed fiberoptic sensors and systems will be tested *in vitro* to assure overall compliance with stated product requirements.

METRICOR, Inc. plans to license this sensor technology to one or more catheter companies for use in next-generation, disposable, "smart catheter" products. The licensee will be responsible for integrating these sensors into catheter products, conducting necessary clinical trials, product manufacturing, and product sales and service.

Title of Project: Teaching Diabetes Self-Control with Computer Assistance
Principal Investigator: Margaret C. Yarborough
Awardee Organization: Pharmacy Consultation Services
748 East Chatham Street
Cary, NC 27511
Telephone Number: (919) 469-5229
Awardee Number: 2 R44 DK35546-02A1

The Diabetes in Self-Control (DISC) system is a comprehensive microcomputer-based system to facilitate patient self-control of insulin-requiring diabetes mellitus. DISC consists of a data management and review system, diabetes education modules, and diabetes problem solving and goal setting. A pocket computer ("electronic log") will prompt DISC users to record information about blood glucose levels, insulin, weight, diet, exercise, and emotional and physical stress. The log will be periodically interfaced with the microcomputer to transmit data for compilation and subject review.

The diabetes education component of DISC will be organized into three broad levels (survival skills, management skills, and life-style changes) to enhance subject ability to self-pace learning. Additional graphics will be added to the text. The education component developed in Phase I for adolescents will be modified for adults. Readability will be at the fourth-grade level.

There will be two 6-month experimental periods. Fifty insulin-dependent adolescents and 30 insulin-requiring adults will be equally divided into DISC and no-intervention control groups. The effectiveness of the DISC system for newly diagnosed adolescents will be evaluated with 5 to 10 subjects. Measures evaluated will include: glycosylated hemoglobin, frequency and levels of blood glucose tests, diabetes knowledge, management behaviors, and subject participation in diabetes control.

Title of Project: Accustic Monitor for Laser Lithotripsy
Principal Investigator: David I. Rosen, Ph.D.
Awardee Organization: Physical Sciences, Inc.
Research Park, P.O. Box 3100
Andover, MA 01810
Telephone Number: (617) 475-9030
Awardee Number: 2 R44 DK37203-02

The objective of the proposed research plan is to continue efforts begun in Phase I to develop an acoustic monitoring device for laser lithotripsy. *In vitro* results to date have shown considerable promise for acoustic monitoring as an extremely valuable, nonvisual diagnostic tool for laser fragmentation of urinary and biliary tract calculi. The attendant acoustic signatures generated have been shown to be useful for guiding and pinpointing the laser-delivery fiber, indicating an appropriate choice of laser-power level, and discriminating the irradiation of a stone from healthy, soft tissue surrounding it. An acoustic monitoring system providing such information to the clinician performing laser lithotripsy will be of great value, especially in those applications where vision is problematic.

The specific objectives of the Phase II effort are: (1) to complete critical remaining studies to better quantify and more firmly establish the correlation of the acoustic signatures with a wide range of relevant laser irradiation and stone conditions; (2) to use this knowledge to guide the engineering design requirements for an acoustic monitoring device; (3) to arrive at a prototype design and test it through a series of *in vitro* and *in vivo* studies; (4) to establish final design requirements based on input from practicing clinicians; and (5) to make a prototype device available for piggyback experiments on ongoing clinical trials of laser lithotripsy.

The proposed Phase II program has been designed to provide the necessary research and development for commercializing this device in a Phase III effort.

Title of Project: High-Affinity Ligands for Specific Adenosine Receptors
Principal Investigator: John L. Neumeyer, Ph.D.
Awardee Organization: Research Biochemicals, Inc.
9 Erie Drive
Natick, MA 01760-1390
Telephone Number: (617) 651-8151
Awardee Number: 2 R44 DK37728-02

The nature of the adenosine receptor will be studied using adenosine agonists and antagonists modified for selectivity and possible affinity labeling. Adenosine plays a key role in physiological processes, and currently no selective A_1 or A_2 antagonists have as yet been developed. Selective agonists and antagonists for adenosine receptors could have clinical importance in the treatment of asthma and as diuretics, respiratory stimulants, and central nervous system depressants or stimulants.

The following series of adenosine A_1 and A_2 agonists and antagonists will be synthesized and evaluated: (1) alkyl-substituted xanthines, (2) 8-thienyl-substituted xanthines, (3) 8-cycloalkyl-substituted xanthines, (4) 8-phenylxanthine derivatives—functionalized sulfonamides, (5) thio and dithio xanthines, (6) functionalized 2-arylaminoadenosine derivatives, and (7) fluorescent probes for adenosine receptors.

New products generated in Phase II studies will be further evaluated for possible commercial introduction to the expanding neuroscience community as research tools and evaluated as potential therapeutic agents.

Title of Project: Programmable Rotary Pumps for Gas and Liquid Metering
Principal Investigator: Harold H. Kantner
Awardee Organization: Transcience Associates Inc.
1112 Hinman Avenue
Evanston, IL 60202
Telephone Number: (312) 475-1125
Awardee Number: 9 P44 DK39060-02

A new type of pump that employs resilient rotors—paired gears and rollers—rolling against each other has been patented and demonstrated. Roller/gear pumps have been shown to be especially suitable for precisely programmed flow control of both liquids and gases at difficult low values of flow. The specific aim of continuing research is to extend functional capability and utility for a broad spectrum of laboratory, industrial, instrument, and health-related applications involving gas and liquid sampling or automated metering and proportioning.

Long-term objectives encompass development of 100 percent polymer-fabricated roller/gear pumps that are easily produced at relatively low cost. Continuing research, primarily experimental, is concentrated on (1) reduction of friction among dynamic sealing members; (2) establishment of form factors and parameter ratios optimal for a one-design family of pumps spanning a range of fluid flows extending to 10 liters per minute at pressures to 30 psi; and (3) creation of digital electronic drivers/controliers for program-regulated, pumped-fluid flow under computer control.

The innovative roller/gear pump technology provides a critical basic building block for nonpulsating, positive-displacement control of liquid and gas flows. It can lead to the development of new markets for heretofore unrealizable pump applications. Its potential for more immediate commercialization has been recognized by hospital administrators, by laboratory pump distributors, and by manufacturers of industrial hygiene and health care equipment.

Phase I Contracts

Title of Project: Plastic Film-Supported DNA Sequencing Gels
Principal Investigator: Daniel E. Sullivan, Ph.D.
Awardee Organization: Betagen Corporation
Brookside Park
100 Beaver
Waltham, MA 02154
Telephone Number: (617) 899-3400
Awardee Number: 1 N43 DK72229-00

The objective of the research plan is to develop a process of preparing thin polyacrylamide gels for DNA sequencing, substituting plastic film for glass plates as the supporting material. A process to make plastic film-supported gels with satisfactory electrophoretic properties will allow preparation of ready-to-use gels and form the basis of a useful manufacturing process. Commercial availability of preformed gels will eliminate manual preparation of gels for DNA sequencing, a time-consuming and tedious step common to all DNA-sequencing procedures.

Initial studies show that gels formed on a variety of plastics do not provide the resolution needed for DNA sequencing. Evidence suggests incomplete acrylamide polymerization at the gel/film boundary. This research plan describes several experimental approaches aimed at ensuring complete gel polymerization on polyester films. The protocol used for preparation of high-resolution, plastic film-supported gels developed in Phase I of this project will be the foundation of a Phase II proposal for the design and construction of a system to manufacture precast gels. Ultimately, plastic film-supported gels will be sold for use in Betagen Corporation's automated DNA-sequencing instruments and most manufacturers' electrophoresis systems.

Title of Project: Improved Biocompatibility of Peritoneal Dialysis Tubing
Principal Investigator: Shawn G. Dunkirk
Awardee Organization: Bio-Metric Systems, Inc.
9924 West 74th Street
Eden Prairie, MN 55344
Telephone Number: (612) 829-2700
Awardee Number: 1 N43 DK72299-00

The development of miniature dialysis tubing that can be implanted within the body will make possible *in vivo* collection of short half-life metabolites within the interstitial fluid from animals and ultimately humans. However, before safe implantation of tubing can be done, the biocompatibilities of these materials must be improved.

During this project it is planned to covalently attach factors to commercially available dialysis tubing. This is expected to improve its biocompatibility with living systems without impairing dialysis performance. The dialysis performance may be improved by the attachment of some of these compatibility factors to make this technology even more attractive. Bio-Metric Systems, Inc. will demonstrate the covalent attachment of these factors to dialysis tubing, compare the *in vitro* compatibilities of modified and control tubings, and analyze the performance of surface-modified materials.

This Phase I project should establish the feasibility of this technology and serve as the basis for optimization of coupling chemistries and *in vitro* testing during Phase II research.

Title of Project: High-Affinity Monoclonal Antibodies for Endocrinology
Principal Investigator: Willfried Schramm
Awardee Organization: BioQuant of Ann Arbor, Inc.
1919 Green Road
Ann Arbor, MI 48105
Telephone Number: (313) 995-2176
Awardee Number: 1 N43 DK72223-00

The long-term objective of this project is to provide for the endocrine community a collection of specific monoclonal antibodies (MoAbs) with especially high affinity for a number of hormones and receptors being actively utilized in research. The specific aim of this Phase I project is to develop one or more MoAbs with these characteristics for steroid hormones. The resulting MoAbs should be of considerable value to investigators working on many different endocrine research problems. Examples of use include the development of more sensitive and specific immunoassays, the development of anti-idiotypic antibodies useful for receptor isolation, immunoneutralization of hormonal activity, and immunohistochemical localization of hormones.

Development of desired MoAbs will begin by preparation of derivatives of the steroids at selected sites chosen to maximize chances that resulting antibodies will be specific. The derivatives will be conjugated to keyhole limpet hemocyanin, and immunization will be performed *in vivo* using BALB/cByJ mice. Fusion, screening, selection, and analysis will involve procedures to enhance the probability of obtaining high-affinity MoAbs.

Phase II research will involve extending the approach to develop and characterize similar MoAbs to other steroids, peptide hormones and/or growth factors, and their receptors as they become available. Chosen and subcloned MoAbs will then be produced in quantity *in vitro* using a customized in-house bioreactor system.

Title of Project: Automated Equipment for DNA Sequencing
Principal Investigator: Jim Marquis
Awardee Organization: BIOTIX
Commerce Park
Corporate Drive
Danbury, CT 06810
Telephone Number: (203) 790-7880
Awardee Number: 1 N43 DK72230-00

BIOTIX proposes to develop several pieces of instrumentation that will speed the process of DNA sequencing. The approach is to assess the feasibility of automating several steps of the sequencing procedure that are currently accomplished manually. Specific Phase I objectives include the development of prototypes for a unit that will automate the actual sequencing reactions and a unit that will semiautomate the pouring of sequencing gels.

Title of Project: Multipurpose Cloning/Subcloning System
Principal Investigator: Dale M. Roderick, Ph.D.
Awardee Organization: BIOTIX
Commerce Park
Corporate Drive
Danbury, CT 06810
Telephone Number: (203) 790-7880
Awardee Number: 1 N43 DK72227-00

BIOTIX proposes to develop systems for stably cloning small and large DNA fragments that are also optimized for producing a series of overlapping subclones using either the single-stranded or the double-stranded procedure. The vectors will be constructed from existing vectors utilizing a powerful new insertion technique. Success in the construction of these vector systems will lead to the development and production of a series of integrated kits during Phase II.

The specific Phase I objectives are: (1) construction of a vector with a multiple cloning region optimized for both single- and double-stranded subcloning procedures; and (2) modification of the vector to include a cos site to permit up to 40 kb fragments to be stably cloned.

Title of Project: Instrument Channel Fiberoptic Spectroscopy for Gastrointestinal Endoscopy
Principal Investigator: Richard R. Pettijohn, Ph.D.
Awardee Organization: Center for Planning and Research, Inc.
560 San Antonio Road, Suite 105
Palo Alto, CA 94306
Telephone Number: (415) 858-0252
Awardee Number: 1 N43 DK72297-00

The overall objective of the proposed program is to develop a spectroscope suitable for use with gastrointestinal endoscopy. The spectroscope design will utilize a high-intensity light source coupled to one of two optically isolated quartz light guides in a sheathed fiberoptic bundle. The instrument channel of any commercial endoscope will serve to guide this fiberoptic bundle to the area being evaluated. The reflected or fluorescent light from the illuminated tissue will be guided up the second light guide of the fiberoptic bundle and back to the spectroscope where it will be dispersed onto a linear CCD array detector. Subsequent microcomputer spectral analysis and comparison with stored database standards will provide rapid *in vivo* quantitative evaluation of natural fluorophors, administered localizing fluorophors, and/or the tone, hue, and saturation (color) of tissue. These analytical methodologies have significant potential to provide quantification of tissue inflammation and/or early diagnosis of gastrointestinal tumors and polyps.

The Phase I program will consist of the design, construction, and testing of a "breadboard" spectroscope suitable for evaluating the performance specifications of the proposed instrument. Design parameters will be studied and computer-modeled to achieve optimum sensitivity, resolution, reproducibility, and signal to noise. The limitations and capabilities of the proposed methodology will be assessed to evaluate the technical merit and feasibility of the proposed approach.

Title of Project: Fiberoptic Probe for Broad-Band *In Situ* Spectroscopy
Principal Investigator: Bruce Nappi
Awardee Organization: Foster-Miller, Inc.
350 2nd Avenue
Waltham, MA 02254
Telephone Number: (617) 890-3200
Awardee Number: 1 N43 DK72296-00

Recent developments in new glass optical fibers based on zirconium fluoride (ZrF), which transmit light at low losses over a wide bandpass from 200 nm wave in the ultraviolet (UV) spectrum through the visible spectrum out to nearly 5μ wavelength in the mid-infrared (IR) wavelengths suggest the development of a clinical instrument combining these new fibers in a fiberoptic endoscope to perform a broad range of spectral analyses *in situ* to measure physiological parameters.

During the proposed program, UV, visible, and IR capabilities will be demonstrated and evaluated. Specific emphasis will be placed on coupling a Fourier transform infrared (FTIR) spectrometer to the fiber probe to demonstrate how this technique could become a useful clinical method for the early detection of cancer in the esophagus, colon, and other hollow organs. The Phase I program will concentrate on the demonstration of a working lab system employing all elements necessary for a clinical device.

Title of Project: Cloning and Expression of Human TSH
Principal Investigator: Scott C. Chappel, Ph.D.
Awardee Organization: Integrated Genetics, Inc.
31 New York Avenue
Framingham, MA 01701
Telephone Number: (617) 875-1336
Awardee Number: 1 N43 DK72222-00

Studies of the biochemistry and physiology of human thyroid-stimulating hormone (hTSH) have been hampered by the recent termination of distribution of pituitary-derived reagents due to potential contamination with the infectious agents of Creutzfeld-Jakob disease and others. Continued acquisition of knowledge about the complex interaction between the endocrine milieu, TSH, and the thyroid gland requires a constant and reproducible supply of a highly purified hTSH preparation. It is possible to employ recombinant DNA technology to produce

this glycoprotein. Integrated Genetics, Inc. recently synthesized the cDNA encoding for the human alpha subunit. A genomic fragment that contains the entire coding sequence for the hTSH beta subunit is available for use. With these clones, it will be possible to genetically engineer them into the eukaryotic expression vector, bovine papilloma virus (BPV).

The mouse epithelial cells (C127) will be transfected with the BPV vectors that contain the genes for the alpha and beta subunits. Cells that transcribe these genes and secrete biologically active hTSH will be identified by radioimmunoassay and bioassay. This proposal describes the method that will be employed to achieve these goals.

Title of Project: Immunosorbent Device for Parathyroid Hormone Removal
Principal Investigator: Gerald Bruno, Ph.D.
Awardee Organization: International Bio Sorbent Technologies, Inc.
940 Carlton Road
Wyckoff, NJ 07481
Telephone Number: (201) 891-0270
Awardee Number: 1 N43 DK72225-00

The primary objective of the project is to develop an immunosorbent device for removal of excess parathyroid hormone (PTH) from the blood of chronic renal-failure patients. The project will involve synthesis of a specific immunosorbent design of a hemoperfusion cartridge and animal testing to assess device efficacy. A successful outcome in Phase I will lead to the evaluation of the device in human clinical trials and eventual commercial utilization in the treatment of chronic renal failure.

Title of Project: Gastrointestinal Endoscopic Optical Fiber Fluorimetry
Principal Investigator: Charles Kershaw
Awardee Organization: I.V.P. Company
7822 Rockhill
Houston, TX 77061
Telephone Number: (713) 640-1704
Awardee Number: 1 N43 DK72295-00

Research on novel gastrointestinal endoscopic optical fiber fluorimetry (GEOFF) sensors is proposed in answer to the emphatic need for significant gains in new and better sensor devices in connection with research, diagnostic, and therapeutic endoscopic procedures.

The merits of promising single- or multistranded and disposable optical fiber fluorimetry sensors configured to augment the fiberoptic endoscopes will be evaluated in answer to a variety of applications, namely: (1) innovation toward more direct and detailed interpretation of tissue fluorescence *in vivo* using dyes such as Rhodamine 123 (RH-123), a mitochondrial-specific dye; (2) adaptations of disposable GEOFF sensors integrated with endoscopic systems to upgrade and extend the diagnostic ability of endoscopic procedures, as well as promote new configurations of advanced endoscopic devices; and (3) implementation of a first generation of "smart" endoscopic devices endowed with "intelligence" functions such as detection, recognition, storage, and manipulation of tissue data obtained from visual and nonvisual spectral cues.

National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Title of Project: Video Acquisition-Based DNA Sequence Generation
Principal Investigator: Harry L. Loats
Awardee Organization: Loats Associates, Inc.
24 North Court Street
Westminster, MD 21157
Telephone Number: (301) 876-8055
Awardee Number: 1 N43 DK72226-00

The purpose of this project is to develop a low-cost system that will increase the speed and efficiency of reading and processing DNA sequencing data. Video-based imaging technology will be utilized for fast acquisition, and adaptations of processing programs will be developed for automated identification.

Medical image analysis system equipment will be used. A video camera will be modified to provide additional depth of data in the desired range. The total system will be used as a test bed for processing program development. Because the system is of modular design, advanced technology hardware components will be substituted when available. Specifications will be developed to interface to commercially available sequence analysis programs and databases. The feasibility of the low-cost, high-speed approach will be evaluated by comparing the reading and processing of a number of sample gels.

A successful Phase I will prove feasibility of the concept. Phase II will be required to convert "breadboard" circuitry to commercially viable hardware and to optimize the hardware and software for ease of use.

Title of Project: A Noninvasive Medical Diagnostic Instrument
Principal Investigator: Seymour M. Monat, D.D.S.
Awardee Organization: Monat Associates
4 Hollis Court
Centerport, NY 11721
Telephone Number: (516) 261-5449
Awardee Number: 1 N43 DK72298-00

By combining endoscopy with near-infrared reflectance analysis, a new medical diagnostic instrument and a new methodology will be created. The instrument will receive data by a safe, *in situ*, noninvasive examination of human tissues and lesions. Data so obtained will be compared with known data stored in a computer memory bank. The development of the new methodology will yield a diagnosis that will be extremely accurate and will have a high degree of certainty. This methodology will substitute objective interpretation for subjective interpretation, helping to de-emphasize the human factor in diagnosis.

This instrument can also be used as a research tool. Because the instrument will measure and record chemical changes in tissues, it may be possible to observe and record the changes that take place when normal tissue changes into a nonmalignant tumor, which in turn becomes malignant.

In genetic research or diagnosis, this instrument may be able to determine defective genes more rapidly and more efficiently than is possible by other methods. As a nonmedical tool, this instrument may be used commercially—for example, in a noninvasive technique to measure the ripeness of melons (the ripeness of which depends upon the sugar content).

Title of Project: Development of Methods for Large-Scale Peptide Synthesis
Principal Investigator: Robert J. Webber, Ph.D.
Awardee Organization: Peptide Laboratory, Inc.
6450 Bay Street
Emeryville, CA 94608
Telephone Number: (415) 233-3307
Awardee Number: 1 N43 DK 72224-00

New methods are needed for the routine production of peptides by solid-phase synthesis on the kilogram scale. Currently, peptides are manufactured on the milligram to gram scale, but this small-scale production results in a very high price for commercially available synthetic peptides. This project will develop the required materials, reagents, and techniques for the large-scale (0.4-mole) solid-phase synthesis of rat atrial natriuretic peptide (ANP), the recently discovered hormone produced by the heart. The methods and reagents developed for the large-scale synthesis of this polypeptide hormone will also be directly applicable to other biologically active peptides. Increasing the size of each batch is the only way by which the cost of synthetic peptides can be lowered.

This project will develop the materials and procedures required for the routine production of synthetic peptides on the kilogram scale. Phase I will focus on the development of the needed solid support, preparation of the protected amino acid that is to be used to derivatize the resin support, and derivatization of the resin with the protected amino acid that will ultimately be the carboxyl terminal residue of the finished peptide.

Title of Project: Serum-Free Medium for Hematopoietic Cells
Principal Investigator: Ronald L. Brown
Awardee Organization: Quality Biological, Inc.
7920 Queenair Drive
Gaithersburg, MD 20879
Telephone Number: (301) 840-9331
Awardee Number: 1 N43 DK72231-00

The long-term objective of this proposal is to develop a serum-free medium that will support the growth and differentiation of hematopoietic cells. The initial research will focus on the development of a serum-free medium that will support the growth and differentiation of erythrocytes, granulocytes, macrophages, and lymphocytes. Specific attention will be paid to the purity of each component and only human compounds will be used where biological components are found necessary. Such studies will employ the in vitro assays that are routinely used for hematopoietic cells.

The initial serum-free medium will be developed for the proliferation of normal human peripheral blood lymphocytes and subsequently modified for bone marrow cells. This approach should not only lead to the development of a serum-free medium but elucidate the role each component plays in hematopoiesis. Phase I will primarily use erythrocytes, granulocytes, and macrophages to gain an understanding of the components that will support proliferation and differentiation of hematopoietic cells.

Phase II will extend this effort to develop a serum-free medium for all the human hematopoietic cells. Such a medium will be useful for standardizing *in vitro* hematopoietic assays and transplantation studies where specific bone marrow populations need to be expanded.

Title of Project: Enhanced On-Line Gel Electrophoresis System
Principal Investigator: Gerald Entine, Ph.D.
Awardee Organization: Radiation Monitoring Devices, Inc.
44 Hunt Street
Watertown, MA 02172
Telephone Number: (617) 926-1167
Awardee Number: 1 N43 DK72228-00

An understanding of genetic information achieved by sequencing DNA is one of the most exciting recent advances in biochemistry. Gel electrophoresis is the most widely used method to achieve this important result.

Typically, the separation of the different molecular-weight fragments in the gel requires several hours, and the gel is then removed from the apparatus and subsequently analyzed to reveal the locations of the molecular bands. When radioisotopes are used as markers, the current method of analysis is to use the gel to expose film over 24 to 48 hours. This is labor intensive, time consuming, and subject to error. An alternative approach is to develop a system that will measure the activity in the bands as the separation is taking place. This will eliminate delays and provide quantitative data in a form that allows easy computer analysis.

To make such systems competitive with the current methods, it is essential to develop a highly efficient technique to detect the beta emitters that are most commonly used. It is proposed to develop a completely new detection system that makes use of a scintillator included in the gel formulation. This will significantly increase the speed and efficiency of DNA sequencing and will be a great help to the important work in many fields, including the study of genetic kidney, urologic, and hematologic diseases.

Title of Project: Specialized Membranes for Concentration of Gastric Peptides
Principal Investigator: Mitchell Klausner
Awardee Organization: Tekmat Corporation
200 Homer Avenue
Ashland, MA 01721
Telephone Number: (617) 881-6771
Awardee Number: 1 N43 DK72221-00

Current systems for concentration of gastric peptides from rats and dogs rely on regenerated cellulose membranes that are implanted into the stomach wall. These membranes block adsorption of the peptides they are designed to carry; only 5 to 30 percent of the bulk concentration is observed.

This research program will develop a new membrane that demonstrates enhanced permeation to charged peptides, such as gastrin-releasing peptide, GRP-10, permitting higher permeation and longer lifetime of the membrane in the stomach environment. This will be accomplished by the development of a suitable membrane substrate, such as polysulfone, designed to specified size to enhance permeation of the bulky proteins. In addition, low-temperature plasma treatment of the membrane will impart desirable chemical functionality to enhance permeation of highly polar species.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Phase I Grants

Title of Project: One-Step Semiquantitative Dipstick Enzyme Immunoassay
Principal Investigator: Melvin J. Swanson, Ph.D.
Awardee Organization: Bio-Metric Systems, Inc.
9932 West 74th Street
Eden Prairie, MN 55344
Telephone Number: (612) 829-2710
Awardee Number: 1 R43 ES04258-01

Bio-Metric Systems, Inc. proposes to develop a semiquantitative, nonlaboratory enzyme immunoassay that is expected to be sensitive, rapid, and convenient to use. This immunoassay will require no instrumentation and is expected to have a single-step protocol: simply dip the apparatus in the sample, wait a prescribed time, and observe the result. The quantity of analyte present in the test sample is measured by observing the location of color in the test apparatus, the number of colored bands being directly related to the concentration. The technology will be developed using paraoxon, an organophosphate insecticide, as a model analyte. The assay would be applicable to both environmental samples and body fluids of humans or animals.

Title of Project: Immunoassays for Saxitoxins
Principal Investigator: Navzer D. Sachinvala, Ph.D.
Awardee Organization: Hawaii Biotechnology Group, Inc.
Box 1057
Aiea, HI 96701
Telephone Number: (808) 487-5561
Awardee Number: 1 R43 ES04345-01

The saxitoxins are neurotoxins and are among the most potent nonprotein toxins known. Several thousand cases of paralytic shellfish poisoning occur worldwide each year, with a case-fatality rate approaching 10 percent. Since there is no antidote for such poisoning, avoidance of contaminated material is the only means of control.

The currently accepted method of detecting saxitoxin and its natural derivatives is by mouse bioassay. Alternative methods have been sought, but each has one or more significant drawback. Immunoassays appear to be the most promising method to date. Current limitations of immunoassays are lack of ability to detect all toxins in the saxitoxin group and problems with interference due to components in the sample matrix. Methods are proposed for generating polyclonal and monoclonal antibodies that will enable detection of all of the saxitoxins.

Phase I will focus on the preparation of two different neosaxitoxin haptens and the demonstration of an immunological response in mice or rabbits. Phase II will extend the work and culminate in the development of suitable nonradioactive immunoassays. In addition to use in saxitoxin immunoassays, the antibodies produced may have additional applications as therapeutic agents in cases of paralytic shellfish poisoning.

Title of Project: A New Low-Cost Radon Sampler
Principal Investigator: Joseph Lindmayer, Ph.D.
Awardee Organization: Quantex Corporation
2 Research Court
Rockville, MD 20850
Telephone Number: (301) 258-2701
Awardee Number: 1 R43 ES04257-01

Radon found in indoor air presents a greater radiological health hazard to the greatest population than any other radiation source. Quantex Corporation's objective is to develop a very low-cost, featherweight, mailable, alpha-particle dosimeter medium that can be employed by the general population at any site. The proposed medium is a thin material that maintains trapped electrons at alpha particle impact sites for extremely long times, but will scintillate visible light when illuminated by near-infrared (common GaAs laser diodes, LED's, etc.).

The proposed effort would generate and quantify the performance of experimental samples of Quantex's unique electron trapping (ET) materials in appropriate alpha-transmissive thin-film envelopes to demonstrate feasibility. Phase I will explore the optimum ET material composition and sample fabrication for alpha-particle selectivity, photomultiplier and infrared diode configurations, and "erasing" requirements. Initial cost analysis and amenability to mass manufacturing will be studied and summarized.

The proposed approach would revolutionize radon progeny site sampling, and require relatively inexpensive apparatus at central counting stations. Commercial application would be widespread for dwellings and offices, and could also be very significant for mining personnel.

Title of Project: Identification of Genetic Lesions Leading to Mutations
Principal Investigator: Jay M. Short, Ph.D.
Awardee Organization: Stratagene Cloning Systems
11099 North Torrey Pines Road
La Jolla, CA 92037
Telephone Number: (619) 535-5431
Awardee Number: 1 R43 ES04484-01

Stratagene Cloning Systems has initiated development of a shuttle vector system for the detection and characterization of chemical-induced mutations in transgenic mice. Mouse strains have been developed with an integrated bacteriophage λ genome containing target genes that permit rapid detection of mutations. Several modifications of this integrated λ vector are proposed that will allow rapid DNA sequence analysis of mutations within the target gene (*lac* 1 repressor gene).

After exposure to a mutagen, DNA samples are prepared from mouse tissues. Phage DNA is recovered directly from the mouse genomic DNA utilizing Stratagene Cloning Systems' λ packaging extracts. After plating, phage-containing mutations within the target are easily identified by color assay. Next, the mutant target gene is automatically excised from the λ phage and converted into a plasmid utilizing specific sites in the λ phage and replication proteins derived from the bacteriophage M13. The class of vectors incorporating this conversion process has been termed λ ZAP.

The new mutagenic test vector will be constructed and then microinjected into mouse embryos. Mouse strains containing this novel shuttle vector will be used for rapid, detailed *in vivo* analysis of suspected chemical mutagens.

Phase II Grants

Title of Project: *In Vivo* Total Body Lead Analysis by X-ray Fluorescence
Principal Investigator: Frederic L. Milder, Ph.D.
Awardee Organization: ABIOMED
33 Cherry Hill Drive
Danvers, MA 01923
Telephone Number: (617) 777-5410
Awardee Number: 2 R44 ES03918-02

An estimated 600,000 children under 6 years old have elevated blood lead levels, with 5,000 per year undergoing treatment. In adult medicine, increased total body burden of lead has been associated with the development of kidney disease, hypertension, gout, and neurologic disease. The estimated population affected is in the tens of thousands, but there is no generally available technique to measure total body-lead burden.

This proposal describes development of a technique using x-ray fluorescence in a transmission geometry to measure total lead, *in vivo* and noninvasively. Experiments will investigate the distribution of lead bone stores in cadavers. Results will be used to design and build a prototype lead-measurement machine for adults. Pilot studies will validate the technique clinically. Design of a pediatric machine will also be undertaken. Ultimately, the machines will be useful as (1) diagnostic tools in determining the presence of lead poisoning and elevated levels of body lead; (2) monitoring devices in following the progress of chelation treatment; and (3) screening devices to complement or replace erythrocyte protoporphyrin testing in children and to do epidemiologic studies in adults and children.

Title of Project: Carcinogenesis Information for Environmental Substances
Principal Investigator: Mildred R. Green, Ph.D.
Awardee Organization: Technical Database Services, Inc.
10 Columbus Circle, Suite 2300
New York, NY 10019
Telephone Number: (212) 245-0384
Awardee Number: 2 R44 ES03916-02

The objective of the proposed research is to establish an integrated and easily accessible database containing factual information on carcinogenic and physical-chemical properties and environmental fate of substances that are or might be carcinogenic. The new database, to be called Carcinogenesis Information Database of Environmental Substances (CIDES), with its associated software, will be suitable for online search and retrieval and as machine-readable products for scientists and health officials in public, private, and academic sectors.

CIDES will include information from existing databases and will go beyond them by (1) providing innovative summary information (carcinogenicity ratio) giving the likelihood and the strength of the evidence that a substance is a carcinogen; (2) combining physical-chemical properties and environmental fate information with carcinogenicity and short-term test data into a single source; (3) increasing the number of substances and including radioactive compounds and physical agents; and (4) providing negative results of adequately conducted biological tests for each study extracted into the database.

In Phase I, the feasibility of the work was established successfully by constructing a prototype database for 10 substances. Implementation of Phase II will proceed with the goal of compiling information for over 1,000 substances and designing an online, user-interactive access system.

Phase I Contracts

Title of Project: Molecular Analysis of TK and HPRT Gene Mutations in L5178Y Mouse Lymphoma Cells
Principal Investigator: John Hozier, Ph.D.
Awardee Organization: Applied Genetics Laboratories, Inc.
1335 Gateway Drive, Suite 2001
Melbourne, FL 32901
Telephone Number: (305) 768-2048
Awardee Number: 1 N43 ES72003-00

Applied Genetics Laboratories, Inc. proposes to utilize newly developed molecular genetic techniques to analyze the spectrum of mutagenic events that occur at the TK and HPRT loci in mouse L5178Y cells. The purpose of these studies is to determine if the spectrum of genetic abnormalities registered at these loci is a function of the heterozygous/homozygous nature of the gene loci involved, and to compare the spectrum with the known mutagenic events that occur in humans. Because such mutagenic events are important in the development of human diseases (including birth defects and cancer), the demonstration of a similar potential for registering mutagenic damage in *in vitro* assays is essential in the design of mutagenesis assays, and is likely to contribute significantly to the understanding of the relationship between *in vitro* mutagenic potential and human genetic disease.

Phase I of this project will deal with the adaptation of recent molecular genetic technical developments to analysis of mouse L5178Y cells (at the HPRT and TK genes), while Phase II will provide a full-scale analysis of the hemizygous HPRT gene and the TK gene in both the heterozygous and the hemizygous situations.

Title of Project: Microencapsulation of Unstable Chemicals for Rodent Feed
Principal Investigator: E. S. Nuwayser, Ph.D.
Awardee Organization: BIOTEK, Inc.
21-C Olympia Avenue
Woburn, MA 01801
Telephone Number: (617) 938-0938
Awardee Number: 1 N43 ES72002-00

The overall objective of the project is to develop microencapsulation procedures and formulations for stabilizing the properties of chemicals that are unstable under normal environmental conditions. The stable microcapsules will be mixed with rodent feed, and the chronic toxicity of the chemicals will be evaluated.

During Phase I, microcapsules will be prepared from vitamin A (retinol). This chemical was selected as a model of an unstable test chemical that undergoes rapid photodecomposition. A new, microfluidized bed process developed by BIOTEK, Inc. will be used to produce true wall/reservoir microcapsules. The microcapsules will be evaluated for *in vitro* availability, surface morphology, drug content, and size distribution. Their stability will also be evaluated by storage under humidity and light conditions. The most promising microcapsule formulation will be tableted with ground-up rodent feed and administered to rats to determine taste acceptance and bioavailability of the drug. The microencapsulation process will be scaled up by preparing a 800-gram batch of microcapsules from all-transretinol acetate. This drug was selected for scale-up purposes only because it is similar to but significantly cheaper than vitamin A.

The Phase I studies will provide the basis for further development of the process in Phase II and the microencapsulation of other unstable chemicals whose chronic toxicity must be determined by NIEHS.

Title of Project: GENE*DETEQ: Molecular Screening and Analysis of Mutational Risk
Principal Investigator: Janice L. Smith, Ph.D.
Awardee Organization: Southwest Foundation for Biomedical Research
P.O. Box 28147
San Antonio, TX 78284
Telephone Number: (512) 674-1410
Awardee Number: 1 N43 ES72001-00

A long-term objective of the Southwest Foundation for Biomedical Research is to provide services for detection and prevention of mutation in humans resulting in genetic disease and cancer. It is extending its services from identification of chromosomal aberrations in patients to molecular screening and characterization of mammalian gene mutations. Specifically, in Phase I it is proposed to develop a molecular genetic method, GENE*DETEQ, for the detection and analysis of mutations of the mammalian hypoxanthine-guanine phosphoribosyltransferase gene (*hprt* gene) at the DNA sequence level.

GENE*DETEQ is based on the sensitivity of mRNA: RNA probe duplexes to RNAse cleavage at sites of single-base mismatches. Therefore, GENE*DETEQ permits rapid detection and precise identification of point mutations in this very large gene at a modest cost. Application to other genes should be possible with further research and development. In Phase II, GENE*DETEQ will be used to study molecular specificity of classical model mutagens and suspected mutagenic agents in the environment. The use of GENE*DETEQ in conjunction with well-defined mammalian cellular mutation assays will provide scientifically sound applications by industry and government for public protection from exposure to environmental agents.

Phase II Contracts

Title of Project: Modified Mouse Lymphoma Cell Mutagenesis and Cytogenetic Assays
Principal Investigator: Ann D. Mitchell, Ph.D.
Awardee Organization: Genesys Research, Inc.
2520 Wyandotte Street
Mountain View, CA 94043
Telephone Number: (415) 968-3635
Awardee Number: 1 N44 ES71004-00

Phase II research is proposed to characterize and evaluate a modified L5178Y mouse lymphoma (ML) cell mutagenesis assay that appears to be more efficient and reliable than the standard mouse lymphoma mutagenesis assay (MLA). This modified assay was developed and utilized in Phase I to test chemicals that had been reported to be positive in the standard MLA and negative for the induction of chromosomal aberrations (CA) in Chinese hamster ovary (CHO) cells. Also during Phase I, these same chemicals were tested for the induction of CAs in ML and CHO cells. The same exposure conditions were used for the cytogenetic assays as for the mutagenesis assays, and perfect concordance of results was obtained, i.e., previously negative chemicals were now positive in the CHO CA assay as well as in the ML CA assay, and more CAs were observed in ML cells than in CHOs.

Phase II research will include the characterization and evaluation of the modified CHO CA assay and the new ML CA assay. Chemicals selected for evaluation in these three assays will be primarily from 23 chemicals previously yielding discordant results between the standard MLA and the CHO CA assay out of a group of 73 chemicals tested for the National Toxicology Program.

National Institutes of Health
National Institute of Environmental Health Sciences

Title of Project: Metabolic Activation, Cytotoxicity, and Locus Specificity in Human Cell Gene Mutation Assays

Principal Investigator: Bruce W. Penman
Awardee Organization: Gentest Corporation
6 Henshaw Street
Woburn, MA 01801
Telephone Number: (617) 935-5115
Awardee Number: 1 N44 ES71001-00

Gentest Corporation proposes to extend its investigations into whether the ability of chemicals to induce gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells is indicative of the ability to induce gene mutations in human cells. Chemicals of known mutagenicity in mouse lymphoma cells will be examined for mutagenic activity in TK6 human lymphoblasts at the thymidine kinase and hypoxanthine-guanine phosphoribosyltransferase loci.

This program has three parts: examination of the role of the respective activation systems in disagreements with regard to mutagenicity in the TK6 and L5178Y cell systems, examination of the role of cytotoxicity in statistically significant but weak mutagenic responses that are observed only with cytotoxic treatments, and examination of the gene locus specificity of the above effects. Protocol modifications to overcome any discovered untoward effects, particularly with regard to the influence of cytotoxicity, are proposed.

Title of Project: Technology for Improving *In Vitro* Mammalian Cell Culture and Tests

Principal Investigator: Edwin D. Trautman, Ph.D.
Awardee Organization: Microdrop/Acorn
Village Green
Sudbury, MA 01776
Telephone Number: (617) 443-3223
Awardee Number: 1 N44 ES71011-00

Microdrop/Acorn proposes research and development directed toward significantly improved *in vitro* mammalian cell culture. The proposed work may lead to a general capability to better culture mammalian cells, and also to automation of quantitative *in vitro* testing capability for potentially genotoxic compounds. Large numbers (e.g., 10^9) of cells can be used with an instrumentation system based on optical measurements and rapid computation.

NATIONAL EYE INSTITUTE

Phase I Grants

Title of Project: Retinopathy Treatment: Heparin-Targeted Antiangiogenesis
Principal Investigator: Allan Fenselau, Ph.D.
Awardee Organization: ANGIOGEN, Inc.
107 Lakefront Drive
Hunt Valley, MD 21030
Telephone Number: (301) 667-6880
Awardee Number: 1 R43 EY07035-01

Proliferative retinopathy, or ocular disorders characterized by abnormal retinal neovascularization, presents a serious challenge in ophthalmology. Conventional treatments—laser photocoagulation and vitrectomy—retard but do not necessarily abolish neovascularization and, in the process, produce significant side effects that limit their usefulness. In the proposed studies, the concept of heparin-targeted antiangiogenesis will be applied to the design of drugs for treating proliferative retinopathy. The premise of this approach is that heparin (or a heparin fragment), as a potentiator of angiogenesis and antiangiogenesis, can be used as a delivery vehicle for depositing angiogenic effectors at specific target cells.

During Phase I studies, a series of covalent conjugates of known angiogenic effectors and heparin (or heparin fragments) will be prepared and tested for their antiangiogenesis therapy potential. Various effectors, such as a brain-derived angiogenic polypeptide, an angiogenic inosine derivative, and an angiostatic steroid, will be covalently attached to heparin (or heparin fragments) using published procedures. The activities of the conjugates as well as appropriate mixtures of the conjugate components will be examined in an angiogenesis assay on the chicken chorioallantoic membrane and in *in vitro* assays that display features of the angiogenesis process, namely vascular endothelial cell migration and proliferation.

Title of Project: Research for Development of a Full-Page Braille Display
Principal Investigator: Mel J. Raab
Awardee Organization: Automagic Control Corporation
P.O. Box 35741
1441 South Beverly
Los Angeles, CA 90035
Telephone Number: (213) 552-2101
Awardee Number: 1 R43 EY07466-01

Research necessary for the development of a "point and read" dynamic full-page Braille display is proposed. The display will feature single hand control and will allow reading speeds comparable to those that can be attained with embossed Braille. The display will be designed for use with a computer or terminal and will show the entire screen's contents.

The proposed research will be conducted in two areas: the first will determine the maximum tactile perceptual acuity of Braille readers; the second will be development of the basic design and testing of a display device that can safely provide the determined dense tactile stimulation to the general population of Braille readers. It is expected that the cost of the resulting full-page display will be less than current costs for 20-cell Braille displays, and it will have additional capability for the display of graphics. Reliability is expected to be very high due to the minimum use of moving parts.

Title of Project: Long-Pulse UV Laser and Optical Catheter for Vitrectomy
Principal Investigator: Rafael Sierra, Ph.D.
Awardee Organization: Candela Laser Corporation
530 Boston Post Road
Wayland, MA 01778
Telephone Number: (617) 358-7637
Awardee Number: 1 R43 EY07471-01

Vitreoretinal disease is a major cause of blindness. Current surgical vitrectomy utilizes mechanical cutting devices. However, mechanical removal of the vitreous may be complicated by insufficient tissue cutting and/or inadvertent traction on the retina, resulting in retinal tears, detachment, and hemorrhage.

In this grant application, a long-pulse ultraviolet (UV) laser is proposed for vitreous cutting without harm to surrounding intraocular structures. The extremely short penetration depth of UV light in tissue will enable precise and controlled ablation of vitreous membranes. This laser, as well as an optical catheter system to deliver the laser light and to suction ablated material, will be developed by Candela Laser Corporation during the Phase I period. The device will then be evaluated in an animal model, and a treatment protocol will be developed in collaboration with the Massachusetts Eye and Ear Infirmary.

Title of Project: Hydrogen Fluoride Chemical Laser System for Corneal Microsurgery
Principal Investigator: William Q. Jeffers, Ph.D.
Awardee Organization: Helios, Inc.
1822 Sunset Place
Longmont, CO 80501
Telephone Number: (303) 772-3999, (303) 443-0327
Awardee Number: 1 R43 EY07037-01

It is proposed to develop a pulsed hydrogen fluoride (HF) chemical laser system that is specifically designed for use in corneal microsurgery. Laser parameters such as pulse energy, pulse duration, beam quality, and output spectra will be optimized for application in corneal microsurgery. Issues related to use in a medical environment, such as laser size and packaging, fuels and exhaust handling, EMI suppression, and fiberoptic delivery of laser radiation, will be addressed.

The specific aims and objectives of the proposed research are: (1) to determine optical properties and optimal ablation parameters for efficient microsurgical removal of corneal tissue; (2) to determine spatial and temporal resolution and control requirements for optimal tissue removal; (3) to evaluate adjacent tissue damage by histological examination of postirradiated tissues; (4) to develop a prototype HF chemical laser system with refined laser parameters for corneal microsurgery; and (5) to consider catheter delivery of laser radiation by means of a fiberoptic system. The methodology of Phase I work will include modification of a Helios Model PCLI-pulsed HF chemical laser to provide variation of laser parameters, microscale laser/tissue interaction experiments, and pre- and postirradiation characterization of tissue samples.

If successful, the proposed program will be continued in Phase II and III work to develop a new clinical instrument that permits refined corneal microsurgery using safe and effective infrared laser irradiation.

Title of Project: Electroretinographic Test to Monitor Retinal Ischemia
Principal Investigator: Matthew Severns, Ph.D.
Awardee Organization: LKC Technologies, Inc.
2 Professional Drive, Suite 222
Gaithersburg, MD 20879
Telephone Number: (301) 840-1992
Awardee Number: 1 R43 EY07181-01

The objective of the proposed project is to develop an instrument that will generate and analyze a clinical electroretinogram and extract information that is pertinent to assessing retinal ischemia in patients with retinal vascular disease. This device will be considerably easier to operate than existing electrodiagnostic systems and will provide relevant, unambiguous information to the clinician.

The device will consist of a Ganzfeld photic stimulator and corneal electrode, associated electronics, and a microcomputer. A sinusoidally varying photic stimulus will be presented to the patient while recording the electroretinogram. Algorithms encoded in software will determine if a viable signal is being recorded and, if so, will estimate the amplitude of the signal and the relationship between phase lag and frequency. These two parameters will be presented to aid the physician in determining whether or not to treat a patient to prevent the development of the blinding effects of retinal or iris neovascularization.

Title of Project: Development of a New Corneal Aesthesiometer and Norms
Principal Investigator: Sidney Weinstein, Ph.D.
Awardee Organization: NeuroCommunication Research Laboratories, Inc.
West Kenosia Avenue
Danbury, CT 06810
Telephone Number: (203) 744-7474
Awardee Number: 1 R43 EY05368-01A3

During Phase I, the creation of a safe, valid, precise, reliable, research prototype instrument for testing the somatosensation of cornea, sclera, conjunctiva, and eyelid is expected. The specific aims of Phase I are to: (1) modify the existing Weinstein Oral Microaesthesiometer to create a new instrument, a corneal microaesthesiometer, for testing corneal somatosensation; (2) demonstrate validity and test-retest reliability; (3) develop norms on a small group of subjects; (4) explore the feasibility of obtaining cortical evoked potentials; and (5) explore, as available in the sample, the effects of age, sex, contact lenses, use of tobacco, and use of alcohol upon corneal thresholds.

The long-term objective is to establish the corneal microaesthesiometer test as an office procedure for screening patients for: (1) systemic, ocular, or corneal problems; (2) for predicting recovery from surgery; and (3) for evaluating ideal ophthalmic dosing on an individual patient basis.

The potential exists for the development of a corneal aesthesiometer that will not injure newly transplanted corneas, that will not elicit apprehension in patients, and that will give valid, precise, and reliable tests. Further, the new corneal aesthesiometer could be used to elicit cortical evoked potentials for the evaluation of infants or of mentally impaired patients. In addition, the following disadvantages of current corneal aesthesiometers will be avoided with this instrument: (1) risk of transmission of infection; (2) inability to deliver subthreshold stimulation; and (3) inducing apprehension in the patient from a visually approaching stimulus.

Title of Project: An Improved QLS Instrument to Monitor Early Cataract
Principal Investigator: Peter C. Magnante, Ph.D.
Awardee Organization: Precision Optics Corporation
22 East Broadway
Gardner, MA 01440
Telephone Number: (617) 630-1800
Awardee Number: 1 R43 EY07491-01

Quasi-elastic light scattering (QLS) has been used to noninvasively detect and quantify the molecular changes associated with the early stages of cataract formation in the living human lens. It is proposed to develop a commercial QLS instrument. To establish feasibility, specific improvements will be made to an existing prototype. The improvements include: (1) better measurement localization accuracy, (2) reduced measurement time, (3) utilization of a calibration standard, (4) easy-to-interpret measurement results based on a universal linear cataract-grading scale, and (5) use of a simpler and less expensive signal processor.

Many commercial applications exist for an instrument that provides a reliable, noninvasive measurement of early cataractogenesis *in vivo*. To provide such a measurement capability has long been an important goal in human clinical cataract research. Such an instrument is needed for the following purposes: (1) to assess the effectiveness of putative anticataract reagents, (2) to evaluate the cataractogenic role of pharmacologic agents or radiation used in the treatment of systemic disease, (3) to characterize the early cataract in epidemiologic studies of populations subject to differential cataractogenic stress, and (4) to provide a quantitative basis for the decision to initiate surgical or medical treatment of a cataract.

Title of Project: Intraocular Pressure Tracking Through the Eyelid
Principal Investigator: Joseph B. Seale
Awardee Organization: Symtrac
44 Puritan Road
Buzzards Bay, MA 02532
Telephone Number: (617) 759-4901
Awardee Number: 1 R43 EY07038-01

The goal is to develop an instrument for safe, quick, anesthesia-free measurement of intraocular pressure through the lower eyelid. Pressure is indicated by resonant properties of the eyeball. A low-frequency exciter vibrates the eyelid, vibrational energy flow from the exciter is measured, and elicited eyeball responses are measured by ultrasound. Data analysis spanning frequency and pressure variations yields a reliable estimate of intraocular pressure and its time variations.

The project's objectives are to demonstrate an instrument on a mechanical eyeball analog, obtain accuracy data, determine required eye exposure to low-frequency vibrations and ultrasound energy, and evaluate the safety of the device.

Title of Project: A Comprehensive System for Digital Fluorescein Angiography
Principal Investigator: Eric R. Craine, Ph.D.
Awardee Organization: Western Research Company, Inc.
2030 East Speedway, Suite 213
Tucson, AZ 85719
Telephone Number: (602) 325-4505
Awardee Number: 1 R43 EY07170-01

This project will lead to development of a comprehensive system for digital ophthalmological fluorescein angiography. The system is expected to be superior to existing (largely video) systems in several respects: (1) the inclusion of a digital reference library; (2) the maximum efficiency and cost effectiveness of the system due to the psychophysical analysis used in the design; and (3) the system's ability to eventually evolve into a true expert system.

The specific goal of Phase I is the development of a prototype design and implementation of certain segments of the system for further testing. Phase II will involve construction of a complete engineering prototype.

Phase II Grants

Title of Project: Microcomputer Display Magnification for Low-Vision Users
Principal Investigator: Lawrence H. Boyd, Ph.D.
Awardee Organization: Berkeley System Design
1708 Shattuck Avenue
Berkeley, CA 94709
Telephone Number: (415) 540-5535
Awardee Number: 2 R44 EY06033-02A1

A prototype for an inexpensive, software-based display magnification system for the Apple Macintosh was developed in Phase I of this project. It was subsequently completed, tested, and commercially packaged under the name *inLARGE*™, and is now available to institutions and individuals. Its unique approach to display magnification, based on pixel enlargement instead of character enlargement, distinguishes it from other existing devices. This approach gives *inLARGE* the capability to magnify anything on the normal display of any off-the-shelf application, including graphics. Its strong market potential stems from its ease of use, versatility, and low price, compared to other devices.

The current practical limitation is that it is available only on the Apple Macintosh. The objective of this project is to reach significantly larger populations of low-vision users by developing *inLARGE* for the IBM PC and IBM PC/AT.

Title of Project: Improved Biocompatibility of Intraocular Lenses
Principal Investigator: Shawn G. Dunkirk, Ph.D.
Awardee Organization: Bio-Metric Systems, Inc.
9924 West Seventy-Fourth Street
Eden Prairie, MN 55344
Telephone Number: (612) 829-2700
Awardee Number: 2 R44 EY06877-02

Intraocular lens implants (IOLs) have returned vision to cataract patients. The implant provides visual acuity that is not distorted or magnified, as is vision resulting from wearing thick-lensed spectacles or contact lenses. However, as with all other implantable devices, there are problems with the biocompatibility of the synthetic materials with the tissues of the eye.

Inadvertent contact between the lens and the cornea or other eye tissues at the time of implant or while the IOL is being carried by the patient can cause serious and irreparable damage and result in removal of lenses.

During Phase I, Bio-Metric Systems, Inc. covalently attached polymers to IOL haptics and optics, demonstrated improved surface characteristics of modified IOLs in a cadaver eye model, and demonstrated preliminary *in vivo* indications of the acceptance of the modified IOLs in a feline model. During this Phase II project, it is planned to optimize and develop the synthesis and application of the coating polymers, extensively demonstrate the lack of toxicity of these materials, indicate the usefulness of these coatings by *in vitro* tissue culture analyses, and conduct animal implant studies. The favorable results of this project will lead to implants in primates and ultimately to clinical testing. Such lens modification is expected to decrease the complications associated with IOL wear and make the implantation of an artificial lens feasible for even greater numbers of patients.

Title of Project: Horizontal Light-Path Vision-Enhancing System
Principal Investigator: Henry A. Greene, O.D.
Awardee Organization: Ocutech, Inc.
P.O. Box 625
Chapel Hill, NC 27515
Telephone Number: (919) 493-7456
Awardee Number: 2 R44 EY06248-02

This is a clinical trial involving an experimental and a control group to determine whether visually impaired patients prefer the Horizontal Light-Path Vision-Enhancing System (HLP-VES) over a comparable conventional bioptic telescope system currently available. The experimental design will address factors of appearance, weight, and field of view, which have been shown to be important for the acceptance of bioptic telescope low-vision devices.

The HLP-VES is a departure from conventional low-vision aids in that its optics are arranged across the front of an eyeglass frame rather than protruding outward and forward, which adversely affects both appearance and weight. The controlled clinical trial will be run as a 4- to 8-month double crossover study at three clinical sites. The study will select and follow a cohort of 120 adults with low vision who either currently use an existing enhancement device or are candidates for such a device. The study will also identify factors that will enhance the design and performance of the HLP-VES device.

Title of Project: Ultrasound System for Ophthalmic Tissue Analysis
Principal Investigator: Udo W. Drews, Ph.D.
Awardee Organization: Sonocare, Inc.
21 Industrial Avenue
Upper Saddle River, NJ 07458
Telephone Number: (201) 825-7550
Awardee Number: 2 R44 EY06024-02

This Phase II program is aimed at developing and evaluating a prototype system for advanced ultrasonic diagnosis of diseases of the eye and their treatment planning and monitoring. It will employ unique techniques to analyze radio-frequency (rf) echo signals obtained by widely used, conventional ultrasound instruments. The system will compare computed results to a disease-indexed database and explicitly display objective, diagnostically relevant information. It will generate new types of tissue images depicting tissue type and regions where treatment-induced changes have occurred (e.g., within radiated tumors). While these techniques are being developed for ophthalmology, the system will function in examinations of other organs when appropriate databases are established.

Title of Project: Electronic Braille Page-Output Device Using Nitinol SMA
Principal Investigator: A. David Johnson, Ph.D.
Awardee Organization: TiNi Alloy Company
2736 College Avenue
Berkeley, CA 94705
Telephone Number: (415) 841-4109
Awardee Number: 2 R44 EY06512-02

TiNi Alloy Company proposes to provide, for nonsighted persons, tactile access to the same kind of information that is available via the visual computer monitor. A page format of refreshable Braille characters will enable a visually disabled person to participate effectively in word processing, computer programming, and related tasks. This device will augment existing aids such as Braille printers, speech synthesis, and single-line Braille character output systems by providing tactile output in which content is related to format.

Braille characters are represented by movable pins. Each pin motion is actuated by a wire of nitinol shape-memory alloy, which is heated by electric current. This mechanism takes little space, provides adequate force, requires modest power, and is inexpensive to manufacture.

In Phase I, a single Braille character was built and tested. Phase II research will be aimed at construction and evaluation of a prototype containing 20 rows of characters, with emphasis on defining user requirements and manufacturing costs.

Title of Project: Textskimmer: A Hand-Held Reader for the Visually Impaired
Principal Investigator: Nikos Asimopoulos
Awardee Organization: Topologic Systems Corporation
P.O. Box 582
Blacksburg, VA 24060
Telephone Number: (703) 951-7070
Awardee Number: 2 R44 EY06245-02

A great need exists for an economical reading machine for use by blind and visually impaired people. A unique device, incorporating a hand-held scanner and associated character recognition logic, allows users to input hard-copy text to computer files for general use and output through a voice synthesizer or Braille output device.

A high-scanning window (1 inch) and a unique patented, velocity-compensation circuit make the hand-held scanner usable by blind persons. The high-scanning window allows for automatic format analysis and makes possible a real-time guidance system that is necessary for visually impaired users.

Another patented technique incorporated in this device provides an automatic enhancement of the scanned document and enables poor-quality text to be read. An inherently font-insensitive recognition logic allows for reliable input of a wide variety of text sizes and styles.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Phase I Grants

Title of Project: Solute-Solvent Interactions in Chemistry and Biology
Principal Investigator: Mortimer J. Kamlet, Ph.D.
Awardee Organization: Advanced Technology and Research, Inc.
3933 Sandy Spring Road
Burtonsville, MD 20866
Telephone Number: (301) 421-1856
Awardee Number: 1 R43 GM38377-01

The "solvatochromic parameter" database will be expanded and solubility, distribution, and toxicology properties (XYZ) of organic nonelectrolytes will be correlated, rationalized, and predicted through linear solvation energy relationships of the form: $XYZ = XYZ_0 + mV/100 + s\pi^* + a\alpha + b\beta$, where V is a measure of solute (toxicant) molar volume, and π^*, α, and β are the solvatochromic parameters that measure solute dipolarity/polarizability, hydrogen-bond donor acidity, and hydrogen-bond acceptor basicity.

Properties to be correlated and predicted include aqueous solubilities and toxicities of liquid and solid solutes, solubilities of liquid solutes in human body tissues and fluids, and equilibrium distributions of liquid and solid solutes (including candidate pharmaceuticals and carcinogens) among these tissues. The correlation equations will provide synthesis guidelines for "targeting" of candidate pharmaceuticals toward or away from specific body organs.

Title of Project: HPLC Absorbance Detector with Retroreflective Array
Principal Investigator: D. Rex Bleeker
Awardee Organization: The Anspec Company, Inc.
50 Enterprise Drive
Ann Arbor, MI 48103
Telephone Number: (313) 665-9666
Awardee Number: 1 R43 GM37885-01

The Anspec Company, Inc. will design and construct a prototype liquid chromatography ultraviolet/visible absorbance detector, employing a retroreflective array in the phase conjugate configuration. The array compensates for static and dynamic refractive artifacts in the optical train. Thermo-optic properties of chromatographic flow cells will be evaluated in order to specify an array correctly, and the optical system will be designed to maximize light throughput to the detector and minimize the effects of nonideal array properties. The instrument will employ only passive components in the optical train.

The performance of the completed instrument will be evaluated and compared to that of recently available absorbance detectors. The information will be used to refine the design and prepare engineering prototypes prior to commercial introduction of the system. It is anticipated that the proposed detector will supersede conventional absorbance detectors where quiet, stable operation is needed.

Title of Project: Computer Folding of RNA Molecules Using Monte Carlo Methods
Principal Investigator: Ahmad Waleh, Ph.D.
Awardee Organization: Applied Sciences Consultants, Inc.
1977 Concourse Drive
San Jose, CA 95131
Telephone Number: (408) 434-6780
Awardee Number: 1 R43 GM36180-01A2

The development of efficient methods for predicting secondary structures of single stranded nucleic acids is of great importance in understanding many fundamental processes in genetics and molecular biology. Presently available energy minimization techniques yield only one structure which is often different from biologically significant RNA secondary structures. Application of these computationally complex algorithms is limited to relatively short RNA strands. Applied Sciences Consultants, Inc. proposes that folding patterns of RNAs be predicted by employing an algorithm based on Monte Carlo methods of statistical mechanics, which includes an annealing procedure.

Monte Carlo methods, in contrast to minimization routines, scan many local minima, calculate statistically averaged properties, and predict melting patterns. These methods are not limited by computer storage requirements and therefore can handle RNAs of the order of a few thousand nucleotides. Preliminary results for small RNAs are presented and a feasibility study is proposed to evaluate the efficiency of the new algorithm, determine melting and refolding of short RNA molecules, and predict secondary structures of selected long RNAs. Long-term goals include generalization and further improvement of the algorithm and the development of a rapid and reliable software for analysis of large RNA segments. Both the method and the results of the proposed studies are expected to be of interest to the scientific and business communities in the health-related areas of pharmacology, genetic engineering, and molecular biology.

Title of Project: Chronolog and Reminder for Dropper-Applied Medication
Principal Investigator: James L. Wolf
Awardee Organization: ATA Corporation
1260 West Bayaud Avenue
Denver, CO 80223
Telephone Number: (303) 722-7704
Awardee Number: 1 R43 GM39030-01

Poor compliance to medication regimens and the resulting ineffectiveness of treatment are major concerns in drug studies and in self-administration of prescribed medication. ATA Corporation develops and markets devices that monitor compliance and improve compliance through reminding and guiding functions.

Improvement of poor compliance is particularly important in the treatment of glaucoma. It is proposed to establish the feasibility of an inexpensive device for reminding, recording, and dispensing small, measured amounts of liquid medication, such as ophthalmic solutions used in the treatment of glaucoma. This device will ultimately consist of a container with a miniaturized recording/reminding unit. Medication is contained in a disposable bladder and pump tube that is inserted into the container. The bladder may be filled by a pharmacist or prepackaged by a pharmaceutical company.

The electronic recording device will record the date and time of dispensing. These data can be extracted later by coupling to a micro-computer interpreter. A prescription may be loaded into the device for reminding the patient, who can recall data on the last time of use, when to take medication, and receive assistance in following the regimen. Compliance will be improved due to the ease in using this dispenser and the monitoring/reminding functions.

Title of Project: Isolation of Albumin by Continuous Affinity Separation
Principal Investigator: Paul van Eikeren
Awardee Organization: Bend Research, Inc.
64550 Research Road
Bend, OR 97701-8599
Telephone Number: (503) 382-4100
Awardee Number: 1 R43 GM37862-01

The proposed work is directed toward the development of a novel and efficient method for the continuous isolation and purification of biomolecules from complex and dilute mixtures. Recent developments in biology allow the design and culture of microorganisms and cells capable of producing specific proteins and enzymes of clinical and commercial importance. Production of these protein products consists of two steps: (1) fermentation of cell culture, and (2) isolation and purification. Although fermentation and cell culture have undergone much recent development, isolation and purification remain the weakest part of the overall process.

The goal of the Phase I program is to establish the feasibility of employing hollow-fiber membranes in conjunction with affinity binding for the purification of proteins. The removal and isolation of albumin from human plasma will be used to evaluate the feasibility of Bend Research, Inc.'s approach. Success in this program will make available a general method for the purification of other commercially important proteins.

Title of Project: Production of Recombinant Proteins in Milk
Principal Investigator: Harry M. Meade, Ph.D.
Awardee Organization: Biogen Research Corporation
14 Cambridge Center
Cambridge, MA 02142
Telephone Number: (617) 864-8900
Awardee Number: 1 R43 GM37355-01

A model system for production of recombinant proteins in milk using mice will be developed in Phase I. This will establish that it is possible to produce novel proteins in milk from mammary tissues. A promoter specific for mammary cells will be used to direct the expression of a test protein that is easily detected. The DNA constructs containing these segments will be injected into mouse embryos. The resulting transgenic mice will be tested for the presence of the new recombinant proteins in their milk.

Those constructs that function in the mouse model system will be injected into bovine embryos in Phase II. The resulting transgenic cattle will be tested for the production of recombinant proteins in their milk. This procedure will establish a methodology by which novel cloned proteins can be produced in cow milk on a commercial basis at a fraction of the cost of current tissue culture techniques.

Title of Project: Fiberoptic pH Sensor for *In Vivo* Measurements
Principal Investigator: Donald E. Gregonis, Ph.D.
Awardee Organization: Biomaterials International, Inc.
420 Chipeta Way, Suite 160
Salt Lake City, UT 84108
Telephone Number: (801) 583-8444
Awardee Number: 1 R43 GM38365-01

The development of a fiberoptic pH probe is proposed using a fluorescent dye immobilized in a hydrophilic gel matrix. The main tasks in this project are: (1) set-up of research instrumentation for measuring and characterizing experimental probes, (2) selection and immobilization of dyes at the tip of the optical fiber, and (3) test pH probes for signal intensity, pH sensitivity, time response, photostability, and leaching stability. The immobilization procedures will be improved and optimized, if necessary, to provide *in vivo* patient blood monitoring for up to 3 days without recalibration.

In Phase II, this pH probe will be incorporated with a second catheter containing a gas permeable membrane. This second catheter will withdraw O_2 and CO_2 gas from the patient's blood and the gas concentrations will be quantitated using gas-sensing laser Raman spectroscopy. The laser light source will also be used to excite the pH-sensing fluorescence probe. This approach will provide real-time pH, pO_2, and pCO_2 measurements for critical care monitoring.

Title of Project: Polymeric Materials to Minimize Cell and Tissue Adhesion
Principal Investigator: Donald E. Gregonis, Ph.D.
Awardee Organization: Biomaterials International, Inc.
420 Chipeta Way, Suite 160
Salt Lake City, UT 84108
Telephone Number: (801) 583-8444
Awardee Number: 1 R43 GM37858-01

Using the mouse peritoneal implant model, materials will be evaluated for their biocompatibility. The objective of this study will be to develop materials with minimal tendency for cellular and tissue adhesion. Polyurethanes and silicones, materials widely used in biomedical device fabrication, will be synthesized or modified to yield a high concentration of polyether functionality at the polymer surface. Previous studies have shown that the polyether surface provides these desirable characteristics. The materials will be evaluated up to 4 months of implantation time.

Phase II developments will include addressing the long-term stability of the silicone materials, if necessary, to provide covalent attachment of the polyether functionality at the surface upon curing. Long-term animal studies will be directed toward evaluating the effectiveness of the materials over time. These animal studies will use protocols directed toward specific implants and will be done in cooperation with companies already producing soft-tissue implant devices.

Title of Project: The Dithiasuccinoyl Methodology for Peptide Synthesis
Principal Investigator: Derek Hudson, Ph.D.
Awardee Organization: Biosearch, Inc.
2980 Kerner Boulevard
San Rafael, CA 94901
Telephone Number: (415) 459-3907
Awardee Number: 1 R43 GM38946-01

At present, progress in peptide synthesis is limited by the rigorous purification and characterization processes that are necessary in both of the two currently accepted peptide synthesis methods. Biotechnology, as well as biochemical and pharmaceutical research, will benefit from the introduction of a new method of peptide synthesis that uses mild reagents. It is believed that introduction of a range of dithiasuccinoyl (Dts) amino acids, and ancillary

reagents, will provide a high-yielding, racemization-free method of synthesizing highly pure peptides, with consequent dramatic improvements in productivity and the complexity of peptides accessible by chemical synthesis.

In Phase I of the research, methods suitable for large-scale commercial preparation of Dts= derivatives will be developed, and studies will be performed on the automatic synthesis of a challenging sequence to confirm the suitability of the procedure. In Phase II, a novel automatic peptide synthesizer designed specifically to exploit the merits of the method will be developed, as will be methods to synthesize these derivatives in multikilogram amounts.

Title of Project: A Novel Instrument and Method for Amino Acid Analysis
Principal Investigator: Ronald M. Cook, Ph.D.
Awardee Organization: Biosearch, Inc.
2980 Kerner Boulevard
San Rafael, CA 94901
Telephone Number: (415) 459-3907
Awardee Number: 1 R43 GM38936-01

A new approach will be developed for performing amino acid analysis of protein hydrolysates. It will employ a unique derivatizing reagent that is capable of reacting with all amino acids in protein hydrolysates. These include proline, cysteine, and tryptophan, amino acids that are typically difficult to quantitate. The amino acid analyzer will be based on a high-performance liquid chromatography (HPLC) system, but will contain an additional component for sample cleanup prior to injection onto the HPLC column. This should eliminate the spurious peaks typically found in prederivatization procedures. The methodology will provide picomole-level sensitivity, short run times, and accurate, dependable results.

An instrument based on this new technology will be useful in biotechnology and medical research laboratories working with both natural and recombinant proteins. The use of proteins is increasing dramatically, particularly in the search for novel peptide vaccines and in the detailed study of antigen-antibody interactions. Phase I will identify unique derivatizing agents, construct a breadboard analyzer, and establish the conditions for amino acid analysis. Phase II will further validate the analytical method with a variety of protein and peptide samples from various sources. A prototype commercial instrument will also be constructed to automate the entire procedure.

Title of Project: Rigid Supports for Solid-Phase Peptide Synthesis
Principal Investigator: Derek Hudson, Ph.D.
Awardee Organization: Biosearch, Inc.
2980 Kerner Boulevard
San Rafael, CA 94901
Telephone Number: (415) 459-3907
Awardee Number: 1 R43 GM38945-01

Preliminary research performed at Biosearch, Inc. has confirmed that modified inorganic materials may have superior physical and chemical properties for attachment and assembly of peptide chains during solid-phase peptide synthesis. These supports are believed to provide a more favorable environment for the chemical reactions involved, and their rigidity is expected to minimize peptide aggregation problems encountered in the synthesis of complex peptides with conventional polymeric supports. Many areas of biotechnology, as well as biochemical and pharmaceutical research, will benefit from the anticipated efficiency of synthesis and purity of products resulting from this innovation. Progress in these areas is often limited by the careful purification and characterization required for the heterogenous products currently obtained.

In Phase I of the research, a wide range of materials will be carefully screened and compared. It is proposed that the best candidate will be used in the synthesis of a variety of peptides. In Phase II, should a suitable choice emerge, a novel, fully automatic synthesizer will be constructed to exploit these advantages.

Title of Project: New Interference Color Slide
Principal Investigator: John Hanlin
Awardee Organization: BioStar Medical Products, Inc.
5766 Central Avenue
Boulder, CO 80301
Telephone Number: (303) 447-1605
Awardee Number: 1 R43 GM39008-01

The new Interference Color Slide proposed for immunoassays produces the desired color changes in a wet state. This technique will bring assays closer to a one-step process than existing technology. Without the rinsing and drying steps, the wet technique will be simpler and faster than ELISA. The entire assay can be contained inside be reflected in the handling time and end costs of the test. Preliminary calculations indicate the wet slide will be three to four times more sensitive than the dry slide; sensitivity will be in the range of 10 ng/cm^2.

After the completion of Phase I, it will be evident if the proposed slide functions properly. A practical assay system will be specified, and a cost estimate can be produced for Phase II. This new technique and research of the market will form a base for commercial development and production.

an impermeable envelope, thereby reducing the risk of contamination. This technique will also lend itself to producing a panel test with a single applied sample.

The inherent accuracy and reproducibility of optical methods and techniques eliminates the dilution series and controls. This advantage will

Title of Project: Simplified Photometric Ellipsometer
Principal Investigator: John Hanlin
Awardee Organization: BioStar Medical Products, Inc.
5766 Central Avenue
Boulder, CO 80301
Telephone Number: (303) 447-1605
Awardee Number: 1 R43 GM39004-01

A new instrument is proposed for the study of monomolecular organic films. This instrument consists of an imaging ellipsometer viewfinder and a one-spot thickness-measuring photometer visible in the viewfinder. With the viewfinder, monomolecular protein spots could be seen on the surface of a slide, so that sample homogeneity and quality could be assessed before the photometer is used. The size of diffusion zones or a particular feature in a large surface area might be seen.

The photometer will have an aiming index in the eyepiece, and use the intensity at that point to measure film thickness (or the mass of the organic film). Operation will be very straightforward, with a computer converting light intensity or organic mass. A CCD camera and an image processing system will be substituted for the single photodiode in the analysis of the technique.

The instrument will be suitable for automation and unattended operation, while retaining full manual capabilities. It will be able to measure all monomolecular protein films, and screen antibody-producing hybridomas for production quality and antibody properties among other applications.

Title of Project: Cell Separation in Electromagnetic Fields
Principal Investigator: Gunter Hofmann, Ph.D.
Awardee Organization: Biotechnologies & Experimental Research, Inc.
3742 Jewell Street
San Diego, CA 92109
Telephone Number: (619) 270-0861
Awardee Number: 1 R43 GM38413-01

A novel cell-separation method utilizing oscillating electromagnetic fields will be investigated. The principle of separation lies in the polarizable nature of the live cells in the electric field. In this method, a suspension of heterogeneous cell mixture is subjected to electromagnetic fields. Theoretical calculation of a model system predicted that unidirectional cell migration occurs. The velocity of migration is determined by the dielectric properties and sizes of the cells. Therefore, cells of different polarization relaxation frequencies and sizes will be sorted into various fractions. The process may be completed within minutes.

The achievement of this proposed method will greatly facilitate the cell-sorting procedure frequently needed in clinical and research laboratories and bioengineering operations.

Title of Project: Lipid Polymer Films — A Novel Biomaterial
Principal Investigator: Thomas L. Branch
Awardee Organization: Biotechnology Associates, Inc.
1904D Nantucket
Houston, TX 77057
Telephone Number: (713) 781-9234
Awardee Number: 1 R43 GM37874-01

Biotechnology Associates, Inc. will develop surface coatings composed of films of polymerized lipids that will be nonthrombogenic and nonadhesive for cells. Thus they may provide useful biocompatible coatings for biomedical devices. Lipid polymer films will also be modified by coupling of adhesion proteins or peptides to provide surfaces with controlled cell adhesion properties in the absence of serum. Such surfaces should be useful for the serum-free growth of cells, especially in the context of expression and isolation of recombinant DNA products in mammalian cell culture.

Title of Project: Quantitative Trace Element Analysis of Microsamples
Principal Investigator: Paul K. Chu, Ph.D.
Awardee Organization: Charles Evans & Associates
301 Chesapeake Drive
Redwood City, CA 94063
Telephone Number: (415) 369-4567
Awardee Number: 1 R43 GM37898-01

Commercially available glow-discharge mass spectrometry (GDMS) and high-performance secondary ion mass spectrometry (SIMS) instrumentation will be evaluated for quantitative trace element analysis of very small biological samples. Submilligram or microliter quantities of bovine serum, bovine liver, and rice flour, certified by the National Bureau of Standards, will be analyzed for the elements Na, K, Ca, Mn, Fe, Co, Cu, Zn, and Se, among others, as a means of sim-

ulating small quantities of typical biological unknowns. Quantitation studies will be performed, using internal standard, standard additions, and isotope dilution methods to assess accuracy and precision as a function of sample size and analytical protocol.

There are many potential health-related applications for quantitative microtrace element analysis in neonatology, nutrition studies, ophthamology, toxicology, and basic physiological research. Conventional techniques such as optical emission, absorption spectroscopy, and electron microprobe analysis are inadequate for these problems. GDMS and high-performance SIMS are ideal candidate technologies because of their very low gram detectabilities (<1 pg and <1 fg, respectively). Substantial modifications to existing instrumentation or procedures in Phase II will probably be required to achieve quantitative trace element analysis in microspecimens comparable to conventional analysis of larger samples.

Title of Project: SIMS Organic Microprobe Feasibility Evaluation
Principal Investigator: Robert W. Odom, Ph D.
Awardee Organization: Charles Evans & Associates
301 Chesapeake Drive
Redwood City, CA 94063
Telephone Number: (415) 369-4567
Awardee Number: 1 R43 GM39005-01

This Phase I research program will evaluate the feasibility of obtaining microanalytical characterization of organic species contained in biological tissue specimens. This evaluation will be performed using state-of-the-art secondary ion mass spectrometry (SIMS), an ion microscope, and microprobe instrumentation. It will determine the optimum SIMS analytical conditions required to generate useful molecular or characteristic fragment ion intensities from selected organic species dispersed on or contained in matrices having a chemical composition similar to dehydrated soft biological tissues. The lateral resolution of these characteristic ions produced in the imaging SIMS analysis will also be determined.

The feasibility of employing submicrometer-diameter ion sources in the molecular SIMS microanalysis of biological specimens will be studied. The utility of a high mass range, imaging time of flight SIMS (TOFSIMS) instrumental configuration for organic microprobe analyses will also be determined. The capability of performing organic species analyses at a micrometer or submicrometer lateral resolution would be extremely useful in biomedical research and possibly clinical medicine. The research described in this proposal could lead to the development of innovative instrumentation of analytical methods for organic microprobe analysis.

Title of Project: Adaptive Control of Automatic Drug Delivery Systems
Principal Investigator: Tien-Li Chia
Awardee Organization: ControlSoft, Inc.
4122 Wyncote
S. Euclid, OH 44121
Telephone Number: (216) 234-5759
Awardee Number: 1 R43 GM36774-01A1

Recent improvements in implantable physiological transducer technology and the availability of low-cost computational power have greatly increased interest in the automated control of physiological parameters in the research laboratory and in clinical therapy. The objective of this research is to develop and evaluate safe and effective adaptive control software for the automatic regulation of therapeutic agents in clinical applications. The use of such software in existing and future automatic drug delivery devices is a potentially powerful tool for physiological research and clinical therapy.

Two types of adaptive controllers will be evaluated in this project. One is a modified version of the self-tuning regulator that has been tested in physiological systems. The other is a recently developed adaptive inferential control algorithm which has several potential benefits for drug control. Both algorithms will be comparatively evaluated in computer simulations and on anesthetized dogs. The simulations will study the simultaneous control of mean arterial pressure and cardiac output.

The significance of this project stems not only from the usefulness of an automated system to control blood pressure, but from other expected drug-delivering applications. This project will result in user-friendly control software and will have commercial potential as part of advanced equipment for operating rooms, intensive care units, and chronic ambulatory drug delivery systems.

Title of Project: Cystolic Ca^{2+} Ionophores for Fluorescence and ^{19}F NMR
Principal Investigator: Margaret E. Langmuir, Ph.D.
Awardee Organization: Covalent Associates, Inc.
52 Dragon Court
Woburn, MA 01801
Telephone Number: (617) 938-1140
Awardee Number: 1 R43 GM38977-01

Intracelluar calcium is currently the subject of widespread interest as a second messenger that triggers and regulates cell activation. A series of improved Ca^{2+}-chelating agents that can be used for nuclear magnetic resonance (NMR) and fluorescence imaging will be synthesized and evaluated for their absorption and emission characteristics as well as their ability to bind Ca^{2+}.

The proposed Ca^{2+} indicators will have improved optical characteristics over currently used quin2 and indo-1, which they resemble structurally except for the fluorophore. In addition, the indicator will be fluorine substituted for ^{19}F NMR detection. The chelator can be used to follow changes in intracellular calcium concentration, $(Ca^{2+})_i$, as a function of time in response to various perturbing influences.

Title of Project: Synthesis of New Fluorophores for Cytosolic Glutathione
Principal Investigator Margaret E. Lagmuir, Ph.D.
Awardee Organization: Covalent Associates, Inc.
52 Dragon Court
Woburn, MA 01801
Telephone Number: (617) 938-1140
Awardee Number: 1 R43 GM38982-01

Covalent Associates, Inc. proposes the synthesis of a new fluorophore for intracellular glutathione determination. The reaction product of the fluorophore with thiols will have longer wavelength adsorption and emission and higher quantum yield than the best cytosolic thiol fluorophore currently in use for cell sorting by flow cytometry. The dye will have the advantage of being cell-membrane-permeable owing to esterified phenol and carboxyl groups which will subsequently be de-esterfied by cytosolic esteriases, thus trapping the indicator within the cell. Therefore, cell loading should occur at much lower extracellular dye concentrations than currently possible. Adsorption and emission properties in both bound and unbound states with glutathione and thiol-containing proteins will also be studied.

Title of Project: A Software Package for Exact Logistic Regression
Principal Investigator: Cyrus R. Mehta, Ph.D.
Awardee Organization: Cytel Software Corporation
137 Erie Street
Cambridge, MA 02139
Telephone Number: (617) 661-2011
Awardee Number: 1 R43 GM38971-01

In many clinical or epidemiological studies, the objective is to relate a binary response variable to treatment, exposure levels, and other covariates. Usually this is done by using a logistic model with the data analysis based on large-sample assumptions. Frequently, however, the sample size is so small or the data structure so sparse as to invalidate these assumptions. For example, studies of cancer etiology, prevention, or treatment often have a small number of subjects. In such cases, small-sample or exact methods of data analysis need to be used.

These methods, although well recognized in statistical theory, have tended to be computationally intensive and therefore considered to be impractical by data analysts. The recent development by Cytel Software Corporation of a computationally efficient, multivariate shift algorithm for these problems has, however, changed the picture and placed exact logistic regression within the reach of the working statistician.

The main goal of this project is to conduct the preliminary development of a user-friendly and widely marketable software package for this algorithm. Specifically, this project will (1) undertake a study of the feasibility of implementing this algorithm on mini- and microcomputers, (2) explore the possibility of attaching the algorithm to existing statistical packages like SAS and EPIC, and (3) lay the groundwork for developing a convenient data manipulation interface for the algorithm.

Title of Project: Electrofusion and Electropermeation of Cells
Principal Investigator: Hilda Liang
Awardee Organization: ElectroCell
Western New York Technology Development Center
2211 Main Street
Buffalo, NY 14214
Telephone Number: (716) 831-3472
Awardee Number: 1 R43 GM38362-01

The technique of electroporation is utilized to permeate cell membranes to introduce drugs or foreign genetic materials into living cells. Electrofusion is used as a new approach to form hybrid cells for genetics studies and for monoclonal antibody production, as well as for drug infusion via liposomes. ElectroCell plans to develop protocols for electroporation and electrofusion of common cell types, based on the physical properties of cells. Prototypes of the electronic cell fuser and porator will be designed according to ElectroCell's protocols. Microscopic, macroscopic, and continuous-flow cell-fusion chambers will be made. The successful development of both hardware and software procedures and formulae will form the basis for commercialization. The biomedical community in Buffalo, New York, provides an excellent environment for biotechnology transfer and feedback, as well as a test market for future expansion.

Title of Project: Ultrasonically Activated Scalpel for Bloodless Surgery
Principal Investigator: Jeffrey Solash, Ph.D.
Awardee Organization: Energy & Minerals Research Company
P.O. Box 389, 964 East Swedesford Road
Exton, PA 19341
Telephone Number: (215) 647-7715
Awardee Number: 1 R43 GM38871-01

Dermatologists and plastic surgeons need to produce well-controlled, bloodless incisions. While the common, cold-steel scalpel provides surgeons with control over length and depth of cut (dependent on individual skills), the surgical field is not bloodless. For many applications, a self-cauterizing blade would be clearly advantageous. Surgical devices such as lasers, electrochemical cauteries, heated scalpels, and ultrasonic probes are currently in use. Disadvantages associated with the use of these devices include tissue damage, scarring, and increased risk of infection. Recently, an ultrasonic aspirator has been introduced. While this aspirator is effective for certain liver resection procedures, it is not effective in cutting through pliable tissue such as stomach walls.

Energy & Minerals Research Company has introduced an ultrasonically activated knife for industrial use called the ULTRAKNIFE™. This tool cuts a wide variety of materials using markedly lower force. Other ultrasonically activated surgical devices induce mild hemostasis with little damage to surrounding tissues. A modified version of the ULTRAKNIFE™ will be a superior scalpel that will also induce hemostasis during surgery. A research prototype, ultrasonically activated scalpel will be assembled based on the findings of the research program and evaluated by the Dermatology Group of the University of Pennsylvania Hospital. If the evaluation is positive, a Phase II program to develop an ultrasonic scalpel will be proposed.

Title of Project: Carrageenan-Stabilized Colloidal Gold Biosensor Electrodes
Principal Investigator: Barbara S. Kitchell, Ph.D.
Awardee Organization: Enzyme Technology Research Group, Inc.
2020 West Main Street, Suite 40
Durham, NC 27705
Telephone Number: (919) 286-0684
Awardee Number: 1 R43 GM38961-01

A growing need exists for new and improved second-generation electrochemical biosensors capable of reliably detecting, monitoring, and analyzing a variety of chemical and biological compounds in the environment, in process streams, and in body fluids. Such sensors would find extensive applications in the prevention, diagnosis, and treatment of many diseases; however, in the United States, electrochemical biosensor-based analyzers have been commercialized for only 11 substances. Major problems in current commercial biosensor design arise from instability, slow response, and lack of direct, efficient electrical coupling between the active biomolecule and the electronic device.

The successful technology of the Enzyme Technology Research Group, Inc. in preparing carrageenan-based support materials offers a viable route to a new biosensor electrode matrix. In this proposal, the goal is feasibility research on the production of a novel carrageenan-stabilized, colloidal gold electrode that meets the needs of second-generation biosensor design. The work will involve investigation of the new biosensor electrode matrix by physical, biochemical, and electrochemical means. If this research is successful, bioelectrodes for advanced, second-generation biosensors that will have good reliability, fast response, and direct, efficient electrical coupling between the active biomolecule and the electrode will be created. These improved sensors can be used in the medical, environmental, and process-engineering fields.

Title of Project: Low-Cost Flow-Through Isoelectric Focusing
Principal Investigator: Stanley M. Hurd, Ph.D.
Awardee Organization: Focus Research
30 Hawthorne Avenue
Hamden, CT 06517
Telephone Number: (203) 281-7166
Awardee Number: 1 R43 GM37889-01

This proposal will evaluate and define the usefulness of a novel approach for the separation and purification of biological components. This approach will be a modification of the isoelectric focusing (IEF) procedure. The modification utilizes pH gradients established by diffusion across dialysis membranes which separate the ampholytes from the species being focused. The procedure has several advantages over existing techniques: it has high capacity and can be used in a continuous flow-through fashion; it is less expensive than other IEF techniques; and the pH gradient may be altered during the focusing run to achieve maximal separation of one or more components from a given starting material.

The specific aims of the proposed research are: (1) to investigate ways to decrease the resolution time of the device, (2) to study the degree to which the pH gradients may be altered during the run by the addition of ampholytes of selected ranges, and (3) to investigate the loading capacity of the system.

Title of Project: Ion-Selective Channels in Polymerized Lipid Monolayers
Principal Investigator: Gary Czupryna
Awardee Organization: Foster-Miller, Inc.
350 Second Avenue
Waltham, MA 02254
Telephone Number: (617) 890-3200
Awardee Number: 1 R43 GM38994-01

The preparation of extended and highly organized, very thin layers of polymers has been an area of intense research interest and is of great relevance to the production of a new generation of ion-selective electrodes having totally nonconventional geometries.

One particularly successful method to obtain large-area, ultrathin polymer monolayers is through polymerization of lipid molecules at the gas/water interface. Polymerized lipid monolayers produced with diacetylenes have been shown to be remarkably rigid, while those with dienoyl are much more flexible. Other work has shown that the addition of gramicidin to some types of lipid films can control the rate of polymerization.

The experiments planned for the Phase I program involve ion-conductance measurements on gramicidin-containing polymerized lipid monolayers of diacetylene and dienoyl. A comparison of both types of monolayers will provide insight into the effect of monolayer rigidity on gramicidin-channel function. Added control over the molecular packing density will be attempted by using either fatty alcohols and/or fatty acids as the polymerized lipids. The functional reconstitution of polypeptide channels has never been attempted before in a polymerized lipid monolayer, where a high degree of film density can be obtained.

Title of Project: *Bacillus* Hosts for Pharmaceutical Protein Secretion
Principal Investigator: Stephen R. Fahnestock, Ph.D.
Awardee Organization: Genex Corporation
16020 Industrial Drive
Gaithersburg, MD 20877
Telephone Number: (301) 258-0552
Awardee Number: 1 R43 GM37880-01

Bacillus subtilis is an advantageous host organism for the production of foreign proteins at low cost because it has the capacity to secrete high levels of proteins into the growth medium. Several proteins of bacterial origin encoded by plasmid-borne recombinant genes have been secreted by *B. subtilis* strains, and *B. subtilis* can secrete several proteins of eukaryotic origin, although this has not been as successful as with proteins of bacterial origin. This proposal is designed to examine the hypothesis that the discrimination against proteins of eukaryotic origin in *B. subtilis* is related to the timing of proteolytic removal of the N-terminal secretion signal peptide, which occurs later, relative to the synthesis of the protein, in bacteria than in eukaryotic systems. Overproduction of the signal peptidase enzyme in *B. subtilis* is proposed, in order to accelerate signal removal from secreted proteins. To accomplish this, cloning of the *B. subtilis* gene encoding signal peptidase is proposed.

The long-term objective of this proposal is to construct *B. subtilis* host strains that can secrete proteins of eukaryotic origin at levels comparable to those achieved for proteins of bacterial origin. Such strains would make possible the production at low cost of proteins of pharmaceutical interest, some of which cannot be produced in active form in currently available microbial systems.

Title of Project: Developmental Toxicology Structure-Activity Equations
Principal Investigator: Kurt Enslein
Awardee Organization: Health Designs, Inc.
183 Main Street East, Suite 50
Rochester, NY 14604
Telephone Number: (716) 546-1464
Awardee Number: 1 R43 GM37344-01A1

Recent assessments of the status of developmental toxicology by the regulatory and scientific communities have identified a need to apply structure-activity relationships (SARs) to existing test strategies. Health Designs, Inc. has developed a statistical SAR model of teratogenicity based on the literature on frank malformations in mammals. This model is being used to estimate the probability of malformations for chemicals that have not yet been tested.

The purpose of the proposed research is to improve on the prior work by assembling a more coherent and detailed database of developmental effects. SAR models of related sets of chemicals, chemicals with common pharmacologic activity, and common biochemical activity will also be developed.

The database and the SAR models thus derived would materially enhance the armamentarium of industrial toxicologists, hygienists, and regulators in pinpointing exposures of concern. The estimates of developmental toxicity potential could also lead to more focused developmental effects-testing of potentially harmful chemicals. The proposed research could also lead to a reduction in the numbers of animals used in reproductive effects-testing.

Title of Project: Characterization and Expression of cDNA Clones Encoding Human Protease Nexin
Principal Investigator: Michael P. McGrogan, Ph.D.
Awardee Organization: Invitron Corporation
515 Galveston Drive
Telephone Number: Redwood City, CA 94063
Awardee Number: 1 R43 GM37891-01

Protease nexin (PN), cDNA clones were isolated from a human fibroblast library using oligomer probes derived from the N-terminal amino acid sequence of the protein. Several full-length clones were characterized and found to be approximately 2,100 bp long. The PN clones contained a 1,260 bp open-reading frame that defines a 401-amino acid protein with a characteristic leader peptide of 19 amino acids. Two of the full-length cDNA clones have been sequenced, and

PNb differ by two amino acids, which is the result of insertion of a three-base codon, CAG, into the coding sequence. This three-base insertion preserves the coding frame, but changes the amino acid sequence for PNa from Arg to Thr-Gly in PNb. The insertion of the triplet may be the result of an alternate splice in the 3′ region of the PN gene.

Current studies will focus on determining the mechanism by which PNa and PNb arise and comparing the biological activities of these PNs. The structure of the PN-I gene will be analyzed to determine if the region encoding the inserted triplet is located at an intron/exon junction as would be predicted by the model for alternate splicing of the precursor mRNA. The cDNA coding the PNa and PNb will be expressed in mammalian cells, and the activities of these recombinant proteins will be studied.

Title of Project: Supercritical Fluid Chromatography Detector Interfaces
Principal Investigator: Douglas W. Later
Awardee Organization: Lee Scientific, Inc.
379 North University Avenue, #104
Provo, UT 84601
Telephone Number: (801) 375-1119
Awardee Number: 1 R43 GM36244-01

Gas and liquid chromatographs are the most routinely used instruments in analytical and clinical laboratories for the analysis of organic compounds. The objective of Lee Scientific, Inc. is to manufacture an instrument that uses supercritical fluids instead of gases or liquids as mobile phases. The ability to significantly affect solute solubility in the supercritical fluid mobile phase by changes in operating pressure is the fundamental principle on which capillary supercritical fluid chromatography (SFC) is based. Of key importance is the improved analysis of high-molecular-weight, polar, or thermally unstable compounds. Therefore, cellular constituents may be more amenable to analysis by SFC than by either gas or liquid chromatography. Furthermore, preliminary work indicates that these high-molecular-weight and polar biological molecules may be detected by direct injection into mass spectrometers or other detectors normally only available to volatile compounds.

This proposal addresses the advantages of supercritical fluids versus gases or liquids in chromatographic instruments and proposes to evaluate the potential of the commercial development of capillary SFC interfaces for chromatographic detectors such as ionization, electron capture, spectrophotometric, and mass spectrometric detectors. The SFC system developed will be optimized for molecules of the type that are of significance in studies of cellular functions and structure.

Title of Project: The Development of an Improved Implantable Displacement Transducer
Principal Investigator: Steven W. Arms
Awardee Organization: Microstrain Company
176 Park Street
Burlington, VT 05401
Telephone Number: (802) 862-6629
Awardee Number: 1 R43 GM37868-01

The goal of this project is to produce a micro-miniature, fully implantable displacement sensor, capable of chronic implantation *in vivo*. The device will incorporate several new features that enhance the general usefulness of the sensor. The device is based on the principle of detection of the proximity of a magnet by a Hall-effect sensor. Phase I of the study is designed to (1) test and improve the coatings of the sensor in a saline environment, (2) miniaturize the device through changes in design of the Hall generator and its lead wires, and (3) enhance performance by using improved magnetic technology. Phase II of the study will involve a multicenter testing of this

new sensor against optical methods, in chronic animal implantation *in vivo*, and eventually in humans *in vivo*.

It is expected that numerous research groups will benefit from the commercial availability of this device. The data obtained from research using these devices will be extremely useful in the understanding and treatment of ligament and tendon injuries.

Title of Project: Development of New Fluorescent Substrates
Principal Investigator: Richard P. Haugland, Ph.D.
Awardee Organization: Molecular Probes, Inc.
4849 Pitchford Avenue
Eugene, OR 97402
Telephone Number: (503) 344-3007
Awardee Number: 1 R43 GM38987-01

Molecular Probes, Inc. proposes to develop improved fluorophores on which to base fluorescent enzyme substrates. The fluorophores will have higher sensitivity than those in current use and are designed to have lower interference from sample autofluorescence. Some of the fluorophores will have spectral properties designed to permit use of low-cost, long-wavelength excitation sources. New ways of quenching background fluorescence from the substrate will be investigated, as will new methods for development and localization of fluorescence in enzymatic products.

The intent of the research is to first improve the spectral properties of the dyes used as a basis of substrates, and to devise unique methods using fluorescent substrates. These new fluorophores and methods will be used to prepare substrates for disease detection and cellular studies.

Collaborative research utilizing new substrates will be supported in several areas. These include monitoring gene incorporation, enzyme development, cell viability and tracing, receptor-mediated endocytic processes, and flow cytometric enzymatic analysis.

Title of Project: Design and Development of Computer Software for the Generation of Artificial Receptors
Principal Investigator: Frank A. Momany, Ph.D.
Awardee Organization: Polygen Corporation
200 Fifth Avenue
Waltham, MA 02254
Telephone Number: (617) 890-2888
Awardee Number: 1 R43 GM38996-01

This project deals with the design, development, and usefulness of computer software products enabling industrial scientists to computationally generate protein-receptor structures around ligands. These programs will help in the screening of analogs in the design of drugs, hormones, and other commercial products. One long-term goal is to reduce the need for expensive animal models in drug development.

The proposed system will use techniques from many different areas of computer science and other disciplines. Software will draw upon techniques from expert systems, database management systems, statistical pattern recognition, dynamic programming, and other areas.

Commercial applications of the proposed software product include: (1) the design of new small-molecular weight drugs in the pharmaceutical industry by rapid screening methods; (2) the design of peptide hormone analogs in the fields of contraception, analgesia, blood pressure, anticoagulants, growth, and others; (3) the design of new antibiotics and antifungals by modeling the bacterial cell wall and other less understood binding sites not usually considered to be receptors; and (4) the design of new antibody-antigen-binding fragments to be utilized in novel testing kits.

Title of Project: Radial Flow Bioreactor for Anchorage-Dependent Cells
Principal Investigator: Barry D. Schwartz, Ph.D.
Awardee Organization: Sepragen Corporation
P.O. Box 5155
Hercules, CA 94547
Telephone Number: (415) 724-5400
Awardee Number: 1 R43 GM38972-01

The purpose of the research is to develop a cell-culture growth chamber for anchorage-dependent cells that is capable of achieving high cell densities and can be easily scaled up. Such a chamber can be used for the economical production of a number of important therapeutic and diagnostic substances that cannot be produced from animal tissue or bacterial systems. The culture chamber will be designed so that there is a transverse flow of culture medium across a packed bed of microcarriers with attached cells. A unique design, based on radial flow dynamics, should minimize the nonoptimal culture-perfusion problems that are characteristic of other large-scale culture methods and should maximize the uniformity of medium delivery and cell viability.

Because anchorage-dependent cells are becoming increasingly important for the production of valuable biomolecules, and because the competitive cell-growth technologies that exist suffer from a number of pitfalls, there appears to be considerable application for this research.

Title of Project: New Chromosomal Jumping Vectors for Gene Mapping
Principal Investigator: William D. Huse, M.D., Ph.D.
Awardee Organization: Stratagene Cloning Systems
11099 North Torrey Pines Road
La Jolla, CA 92037
Telephone Number: (619) 535-5431
Awardee Number: 1 R43 GM38941-01

Chromosomal jumping has been proposed as a rapid technique for ordering large segments of the genome, increasing the speed at which genes associated with hereditable diseases in humans can be isolated. Technical difficulties associated with the construction of the necessary jumping and junction libraries have slowed the successful application of this technique. The most difficult step in the construction of jumping libraries is circularizing extremely large genomic DNA fragments onto a selectable marker in a single reaction.

Stratagene Cloning Systems will develop a novel cloning technology that allows this step to be reduced to a simple circularization without the selectable marker. The selectable marker is added at a later step under conditions that highly favor the desired ligation products. This technology has the additional feature of T3 and T7 RNA polymerase promoters positioned to generate high-specific-activity probes without subcloning or fragment isolation.

Title of Project: New Methods for Synthesis of Fluorescent DNA
Principal Investigator: Richard H. Tullis, Ph.D.
Awardee Organization: Synthetic Genetics, Inc.
10457 Roselle Street, Suite E
San Diego, CA 92121
Telephone Number: (619) 587-0320
Awardee Number: 1 R43 GM37866-01

The goal of this research is to develop reagents and methods for the direct chemical synthesis of fluorescent DNAs destined for use as DNA hybridization probes and in primer-directed DNA sequencing. Recently, Hood and coworkers have developed a primer-directed DNA sequencing technique. DNA probes have also been found to be useful for detecting bacteria and viruses as well as genetic abnormalities. Several companies are currently developing direct fluorescent probes for use in such applications with the ultimate goal of producing rapid, sensitive, and reliable clinical tests. Currently, most synthetic procedures for making fluorescent DNA probes rely on secondary enzymatic and chemical modification. These developments would be speeded by the introduction of methods for direct synthesis of the desired product.

In Phase I, novel fluorescent-labeled nucleotide phosphoramidites will be synthesized that are suitable for use in automated DNA synthesizers. These compounds will be used to synthesize the fluorescent oligonucleotides. The general availability of such compounds should significantly stimulate progress in the use of fluorescent probes as nonisotopic diagnostic and sequencing reagents.

Title of Project: Development of an Ultrasonic Filter
Principal Investigator: Stephen C. Peterson, Ph.D.
Awardee Organization: Technical Research Associates
410 Chipeta Way, Suite 222
Salt Lake City, UT 84108
Telephone Number: (801) 582-8080
Awardee Number: 1 R43 GM38384-01

Technical Research Associates proposes the development of a novel, noncaking ultrasonic filter, a device that uses standard filter membranes placed in an acoustic field to trap and transport particles away from the filter surface. Both solid and fluid particles suspended in a fluid medium may be acted upon by the moving pressure surfaces. Particles sized between 0.5 and 100 micrometers have been transported by this technology. The filter will be used to clear bacteria from reverse osmosis membranes, for desalination, and to improve fermentation process harvesting.

Title of Project: Nondestructive Evaluation of Drugs and Biomaterials
Principal Investigator: Philip R. Brown, Ph.D.
Awardee Organization: Tronac, Inc.
1804 South Columbia Lane
Orem, UT 84058
Telephone Number: (801) 224-1131
Awardee Number: 1 R43 GM38398-01

The objective of this research is to develop a nondestructive technique based on microwatt batch calorimetry to study the degradation of drugs (solid-state and liquid formulations), biochemicals, and biomaterials (e.g., those used in artificial organs). As a research tool, the microwatt calorimeter is complementary to, and provides information unattainable by, more specific methods such as chromatography and spectrophotometry.

The aim of Phase I is to establish the feasibility of using a microwatt calorimeter to study the degradation of solid-state dosage forms of drugs and drug mixtures. The effect of alternative heat sink materials and sample chamber configurations on instrument equilibration, sensitivity, and accuracy will also be investigated. In Phase II, an instrument will be designed based on Phase I results. The new instrument will have sophisticated electronic control and will be used to study a wide range of drugs, biochemicals, and biomaterials.

The successful completion of this investigation will provide researchers with a rapid, accurate, and reliable instrument to measure overall decomposition rates without applying a physical or chemical stress (e.g., dissolution, heating, changes in ionic strength, etc.). Thus, new insights into the degradation process will be achieved.

Title of Project: Technology for Oral Delivery of First-Pass Drugs
Principal Investigator: Glen D. Leesman
Awardee Organization: TSRL, Inc.
50 Enterprises Drive
P.O. Box 7062
Ann Arbor, MI 48107
Telephone Number: (313) 663-4233
Awardee Number: 1 R43 GM37856-01

Strategies for reducing the dosing interval of orally absorbed drugs rely on changing the release pattern of the drug from the delivery system so that the blood level profile of the drug falls within the therapeutic window over the time of the dosing interval. However, for drugs that exhibit first-pass metabolism, the relationship between extent of absorption and bioavailability is nonlinear, thereby leading to reduced bioavailability when drugs are administered at a very low rate into the GI tract.

The specific aim of this proposal is the development of a drug delivery strategy to reduce the oral dosing interval of drugs exhibiting firstpass metabolism while maintaining bioavailability equivalent to the immediate release dosage form. The strategy entails the design and development of a dosage form strategy that will release fractions of the total dose at specified times/sites in the GI tract. In this manner, the bioavailability will not be compromised by the decreasing release rate, as is often seen in conventional sustained-release dosage forms. Propranolol has been chosen as the specific drug to be studied. Propranolol was chosen because its pharmacokinetics are reasonably well understood and it exhibits dose-dependent bioavailability in the normal therapeutic dosage range. Furthermore, there have been reports in the literature of technology developed for the controlled release of propranolol (for example, Inderal-LA) that are not satisfactory with respect to their bioavailability.

Title of Project: A Novel System for Human Hybridoma Culture
Principal Investigator: Amar S. Tung, Ph.D.
Awardee Organization: Verax Corporation
Etna Road, HC 61, Box 6
Lebanon, NH 03766
Telephone Number: (603) 448-4445
Awardee Number: 1 R43 GM38399-01

With the advent of monoclonal antibody technology, it has become clear that there is a growing need to produce human cells and cell products in larger quantities for the treatment of various immunologic, infectious, and neoplastic diseases. Verax Corporation has developed a novel system for the mass culture of murine hybridoma cells, as well as several serum-free media. It is proposed to extend development work to studies of human hybridoma cell culture. Of particular interest is an analysis of the feasibility of adapting several human hybridoma cell lines to the cell-immobilizing matrix material. In addition, it is planned to develop minimal culture medium for the growth and enhanced productivity of these cells when they are immobilized in the collagen matrix.

Preliminary studies with human hybridoma cell lines in batch culture experiments suggest that significant differences exist between human/human and mouse/mouse hybridomas in terms of their growth and immunoglobulin production potential. The conditions that are necessary for efficient production of human monoclonal antibodies will be defined. While this study will utilize human hybridoma cells, it will open the way for successful mass culture of human cells that make various bioactive and safe therapeutics, e.g., lymphokines, immunomodulators, and enzymes.

Title of Project: A Cost-Effective CCD DNA Sequence Reader
Principal Investigator: Eric R. Craine, Ph.D.
Awardee Organization: Western Research Company
2030 East Speedway, Suite 213
Tucson, AZ 85719
Telephone Number: (602) 325-4505
Awardee Number: 1 R43 GM36152-01A1

This project will develop the application of state-of-the-art charge-coupled device (CCD) image detectors to the problem of the automatic analysis of DNA-sequencing gels. Success of this project will result in commercialization of an instrument capable of reading, interpreting, and storing DNA sequence information directly from an autoradiogram of a DNA-sequencing gel. Such an instrument will strengthen the basic and medical research communities.

Phase I of this project will provide experimental data for analysis of the parameters required of a CCD digitizer used in this application. The problems of integrating the physical design of the instrument with the development of software for image analysis will be thoroughly investigated. Algorithms of analysis and initial software will be developed. These data will serve as a basis for the full-scale development of a DNA sequence gel digitizer, including the comprehensive development of related analysis software in Phase II of this project.

Phase II Grants

Title of Project: Porous Microcarriers for Growing Cell Cultures
Principal Investigator: Anton F. Steuer, Ph.D.
Awardee Organization: Biotech Research Laboratories
1600 East Gude Drive
Rockville, MD 20850
Telephone Number: (301) 251-0800
Awardee Number: 2 R44 GM35035-02A1

The long-term objective of this project is the development of cost-effective technology for the manufacture of vaccines and pharmaceuticals from animal cell culture. Phase I research demonstrated the feasibility of growing mammalian cells in porous microcarriers (PMC) made from collagen-glycosaminoglycan cross-linked copolymer. High densities of viable and metabolically active anchorage-dependent MRC-5 human fibroblasts and Chinese hamster ovary (CHO) cells were grown in the PMC, and high concentrations of anchorage-independent hybridoma cells were entrapped. The PMC remained stable during several weeks of stirred-suspension culture of cells.

Phase II research objectives are: (1) to determine the cell-growth kinetics and product-formation kinetics in this material in greater detail; (2) to increase the range of commercially important cell lines that can be successfully cultured in this material; (3) to develop improved methodology to study the growth, viability, and metabolism of cells in the interior of this material; (4) to study mechanisms of cell association with the matrix and mechanisms of mass transfer of nutrients within the matrix; (5) to understand the hydrodynamic behavior of the particles in the culture medium; (6) to demonstrate the use of this material in batch, fed-batch, and continuous culture in process-controlled fermenters; and (7) to understand the factors controlling economic performance.

Title of Project: Analysis of Yeast Glycosylation of a Human Glycoprotein
Principal Investigator: Donald T. Moir, Ph.D.
Awardee Organization: Collaborative Research, Inc.
Two Oak Park
Bedford, MA 01730
Telephone Number: (617) 275-0004
Awardee Number: 2 R44 GM35034-02

Many mammalian proteins with potential pharmaceutical applications are glycosylated by their native host cells. As the carbohydrate on many glycoproteins has been shown to be important for intermolecular recognition and stability *in vitro* and *in vivo*, it may be necessary to produce glycosylated forms of the proteins as pharmaceutical products. Production of such proteins in microorganisms by means of recombinant DNA techniques offers advantages of economy and virtually unlimited supply, and Collaborative Research, Inc. has demonstrated that the yeast *Saccharomyces cerevisiae* accurately glycosylates the proper asparagine residues of the human serum protein alpha-1-antitrypsin (AAT) as it is secreted into the culture broth.

The aim of this proposed work is to determine if the various patterns of carbohydrate added by different yeast strains carrying mutations in the glycosylation pathway (1) provide *in vitro* and *in vivo* stability to AAT beyond that observed for unglycosylated AAT, and (2) raise no new antibodies in an animal model beyond those raised by AAT isolated from human serum. If these results are obtained, this yeast glycosylation and secretion system should allow economical and unlimited production of nonimmunogenic glycosylated AAT and other mammalian glycoproteins.

Title of Project: Development of Optical Sensors Based on a New Membrane
Principal Investigator: Theodore R. Beck, Ph.D.
Awardee Organization: Electrochemical Technology Corporation
1601 Dexter Avenue North
Seattle, WA 98109
Telephone Number: (206) 285-7404
Awardee Number: 2 R44 GM36220-02

Objectives of the Phase II research are to develop a family of miniature, disposable, optical sensors for use in the field of medicine to measure pH, pCO_2, and pO_2. Single-fiber sensors will be designed to meet the performance specifications for *in vivo* measurements in blood, tissue, and gastric fluid for clinical and research applications. The unique combination of chemical and optical properties of a new class of acrylic ion-transfer polymers, developed by Electrochemical Technology Corporation, will be exploited.

Fluorescent dyes will be incorporated in polymer membranes that are applied to the ends of polymethyl methacrylate optical fibers by a simple dip-and-dry technique. Quantitative performance data will be obtained for the sensors and correlated with mathematical models to establish a firm scientific basis for optimization of sensor and system design for specific applications. Potentials for technological innovation include binding of dye molecules in the ion-transfer polymers, developing novel CO_2 and O_2 sensors, and optimizing sensors, optics, and electronics for high performance.

Title of Project: R&D of Improved Li Electrode for High-Energy Batteries
Principal Investigator: M. Eisenberg, Ph.D.
Awardee Organization: Electrochimica Corporation
20 Kelly Court
Menlo Park, CA 94025
Telephone Number: (415) 327-8600
Awardee Number: 2 R44 GM36129-02

Electrochimica Corporation proposes to develop high-energy, rechargeable lithium batteries which would be of great importance to the field of heart pump development and other implantable or portable medical or biomedical devices. Lithium batteries would provide energy densities well in excess of what nickel-cadmium batteries deliver at present. Future progress in this area depends on successful development of a lithium electrode (anode) with desirable rechargeability characteristics. The basic criteria for rechargeability of lithium anodes and anode electrocrystallization are discussed. A multicomponent approach to electrolyte design is described where cosolvent mixing will provide desirable properties as a result of synergistic effects. A strong case for future development of reducible-type cathodes is made, as cathode selection is shown to affect criteria for attainment of desirable electrolytes.

Results of Phase I are presented; electrolytes are described that satisfy the criteria for Li cell rechargeability, including high specific conductivity to enable high discharge rates, a stable potential window, and a high coulombic Li stripping efficiency to enable long cycle life.

Title of Project: Rapid Approaches to the Production of Genomic DNA Probes
Principal Investigator: Kirk E. Fry, Ph.D.
Awardee Organization: Gene Labs, Inc.
871J Industrial Road
San Carlos, CA 94070
Telephone Number: (415) 369-9500
Awardee Number: 2 R44 GM34140-02A1

The study of human genetic disorders at the chromosomal level and of linked families of genes has been hampered by the inability of current methods to handle very large DNA fragments. A series of improved methods will be developed for cloning DNA fragments to sample or cover a region of up to two million base pairs in either direction from a given DNA probe. In conjunction with these methods, procedures will be evolved to isolate highly polymorphic restriction fragments in the vicinity of a given probe and to obtain nested sets of unique-sequence DNA fragments for high-resolution, rapid mapping of the probe by *in situ* chromosomal hybridization. These methods will be applied to developing polymorphic probes saturating the short arms of chromosomes 6 and 11, and the long arm of chromosome 13, and to investigating anomalous genetic behavior in the region of the human MHC that might resemble phenomena seen in the murine t-T complex.

Title of Project: Quantitation of Serum Proteins Using 2-D Electrophoresis
Principal Investigator: Nancy Kendrick, Ph.D.
Awardee Organization: Kendrick Laboratories, Inc.
1202 Ann Street
Madison, WI 53713
Telephone Number: (608) 258-1565
Awardee Number: 2 R44 GM35622-02

Two-dimensional (2-D) electrophoresis is the most effective method known for resolving complex mixtures of proteins. At present, however, the method is seldom used for quantitation of proteins in human serum because of three problems: (1) serum albumin interferes with the resolution of most other serum proteins; (2) losses due to the method are not easily monitored; and (3) computer software for routine clinical analyses using 2-D electrophoresis is not available.

The research proposed in this application is directed toward solution of these problems. A method for removal of albumin from human serum using an immunoaffinity resin will be developed; losses due to the method will be monitored by inclusion of ^{14}C radiolabeled standards, and software for compilation of clinical data will be developed for the IBM AT microcomputer. Eventually it is hoped that about 40 serum proteins can be measured, tabulated, and compared to reference values in a single 2-D gel assay taking 1 to 2 weeks. If so, this newly developed methodology will have widespread application in disease diagnosis and monitoring of therapeutic effectiveness.

Title of Project: Genetic Toxicology Testing by High-Speed Flow Cytometry
Principal Investigator: Andrew M. Tometsko, Ph.D.
Awardee Organization: Litron Laboratories, Ltd.
1351 Mount Hope Avenue, #207
Rochester, NY 14620
Telephone Number: (716) 275-4008
Awardee Number: 2 R44 GM35043-02

Genotoxic chemicals are an existing widespread health hazard to the human population. Advances in genetic toxicology testing have made it possible to assay potential mutagens, carcinogens, teratogens, and clastogens in the environment. However, many currently available mammalian cell tests are costly, time consuming, and labor intensive.

This Phase II research program is directed toward the application of high-speed flow cytometry (FCM) to expedite genetic toxicology testing using mammalian cell systems. The flow cytometer is able to analyze more than 100,000 cells per minute, and thus should be able to provide (1) faster analysis of target cells, (2) larger populations of cells for better statistics, and (3) the potential for automating mammalian cell tests.

The program will focus on experiments designed to optimize and refine the micronucleus assay procedures that were developed during Phase I. The FCM methodology will also be validated with 10 standard clastogens. Finally, FCM methods will be used to expedite the analysis of mutations at select target genes in mammalian cells. Procedures and methods will be designed for routine commercial application of the assays.

Title of Project: Automated Anesthesia Record-Keeping Device
Principal Investigator: Ingvar E. Sodal
Awardee Organization: Masstron, Inc.
5757 Central Avenue
Boulder, CO 80301
Telephone Number: (303) 440-7227
Awardee Number: 2 R44 GM35013-02

The anesthesiologist records observations and events by hand during the course of an operation. Two types of information are recorded. The first type (Type I) involves comments from direct observation of the patient and comments about direct patient intervention such as drug entries. The second type (Type II) involves indirect observation of the patient via various monitors and transducers.

This proposal focuses directly on the development of a device for automatic recording of Type II information, thus relieving the taxing burden of recording these data manually. This device will be unobtrusive to the anesthesiologist, who will simply enter the handwritten notes (Type I information) on the record, while the Type II information will be automatically recorded. The Type II information will be

updated either automatically or on the operator's command. The device features: (1) a combination of handwritten and automatic record-keeping that is efficient and compatible with conventional methods of keeping records; and (2) the capability of interfacing with existing and future monitors. As new monitors become available, they can be incorporated into the system simply by changing a memory module. This update can be performed by the user in the field with minimal effort.

Title of Project: Contribution of Surface Properties to Antibody Immobilization
Principal Investigator: Susan J. Mroczkowski
Awardee Organization: Midwest Research Microscopy, Inc.
5510 West Florist Avenue
Milwaukee, WI 53218
Telephone Number: (414) 527-2260
Awardee Number: 2 R44 GM36267-02

The immobilization of proteins on insoluble surfaces is important in diagnostic instrumentation and *in vivo* monitoring. Improvements in the surface antibody interactions should result in more efficient approaches to immunodiagnostics, and would be especially useful in the field of tumor marker detection where panels of antigens may be needed for proper diagnosis. The proposed research under Phase II is the development of a multiple immunological test with an electronic endpoint.

This new type of device could replace currently used enzyme immunoassay, immunofluorescence, and radioimmunoassay techniques, which are reliable but are slow, tedious, and restricted to single tests per sample. The commercial applications of a multiple test are broad, encompassing cancer and allergy as well as veterinary and forensic diagnostics.

Title of Project: Purification of Marine Oil-Derived Polyunsaturates
Principal Investigator: Nicholas N. Sinchuk
Awardee Organization: Ocean Organics, Inc.
P.O. Box 3598
1080 Kingstown Road
Peace Dale, RI 02883
Telephone Number: (401) 783-4880
Awardee Number: 2 R44 GM36168-02

The specific aim of the proposed project is to develop technologically efficient and cost-effective methods for the separation and purification of multigram quantities of high polyunsaturates (e.g., eicosapentaenoic acid, EPA, C20:5w3; docosahexaenoic acid, DHA, C22:6w3; and esters) from marine/fish oils with the long-term objective of making these and possibly other high polyunsaturates available for a waiting market. The health relatedness of the proposed project is due to the fact that EPA and DHA are modulators of the biosynthesis of prostaglandins and other eicosanoids, of expanding physiologic and pathophysiologic interest in biology and medicine. They affect the physical properties of membrane glycerophospholipids, and there is accumulating evidence that native (Eskimos, certain coastal dwellers) and experimental diets rich in EPA and DHA have antithrombotic and cardioprotective effects.

The methodology for the separation and purification of EPA, DHA, and other marine oil-derived polyunsaturates will focus on state-of-the-art innovations (systems and separation science) in preparative high-performance liquid chromatography. Commercial applications, opportunities, and potential markets will reflect the extensive and prolific research activities and worldwide interest in the leukotriene/lipoxin-precursor polyunsaturated fatty acid cascades and modulation.

Title of Project: Computer-Aided Reflex Measurement System
Principal Investigator: Michael T. Riggs
Awardee Organization: PCB Piezotronics, Inc.
3425 Walden Avenue
Depew, NY 14043
Telephone Number: (716) 684-0001
Awardee Number: 2 R44 GM36130-02

The primary objective of this project is to make and to test clinically a prototype computer-aided, portable myotatic reflex measurement system for use in clinical neurology and clinical research on humans and for laboratory research on large animals. It will consist of a hand-held, instrumented reflex gun containing a microprocessor programmed (1) to deliver reproducible, quantified stimuli ("tendon taps") of graded intensity to the muscle's tendon; and (2) to measure reflex response parameters from the same tendon automatically.

Transducer engineers, a biomedical engineer, and a neurologist will combine their expertise to build a prototype system suitable for commercial development by (1) improving the physical design of the preprototype model of the reflex gun and refining the computer program developed during Phase I; (2) incorporating a microprocessor-based control and data acquisition system into the gun; and (3) testing the resulting product on human volunteers and patients in a clinical setting.

This unique system is technically innovative. It will provide clinicians, clinical investigators, and laboratory investigators with an automated, noninvasive, convenient tool to reliably quantitate all significant parameters of the important tendon stretch reflexes—something not possible before. The resulting data will contribute to the diagnosis and localization of central and peripheral neurologic dysfunction by assessing the overall facilitation and peripheral integrity of the reflex arc, allow one to follow the natural course of certain neurologic illnesses and their response to therapy through changes in the reflexes over time, and quantify some effects of investigative drugs affecting the nervous system.

Title of Project: Construction and Clinical Trials of a ^{31}P NMR Spectrometer Using a Short High-Field Magnet
Principal Investigator: Roger Wheatley
Awardee Organization: Phospho-Energetics, Inc.
3401 Market Street, #320
Philadelphia, PA 19104
Telephone Number: (215) 387-4429
Awardee Number: 2 R44 GM35032-02

Following development of a short 3.0 Tesla magnet system for nuclear magnetic resonance (NMR) spectroscopy that will enable ^{31}P measurements of adult human limbs and heads, and various organs of neonates, it is planned to perfect the magnet system following interface to an NMR spectrometer and isokinetic ergometer. This will be followed by clinical evaluation of the system both for peripheral vascular disease measurement and intraventicular hemorrhage in infants, leading eventually to measurement of hemorrhage in the adult head.

These clinical results will be used for an FDA-approved premarket application. As a low-cost alternative to high-field whole-body NMR systems costing 10 times more, this proposed medical device should gain ready acceptance in the medical community. The clinical trials will take place at the University of Pennsylvania where the completed system is to be installed.

National Institutes of Health
National Institute of General Medical Sciences

Title of Project: New 2-D, Solid-State X-Ray Detector for Biomedical Research
Principal Investigator: Michael Squillante, Ph.D.
Awardee Organization: Radiation Monitoring Devices, Inc.
44 Hunt Street
Watertown, MA 02172
Telephone Number: (617) 926-1167
Awardee Number: 2 R44 GM34181-02

X-ray diffraction is a major tool in the rapidly growing field of molecular biology; the availability of a solid-state, 2-D, position-sensitive x-ray detector would represent an important advancement. Photographic film, the traditional detector, requires expensive and time-consuming analysis. Position-sensitive detectors that have been developed to date also suffer from serious drawbacks.

The development of a 2-D, position-sensitive x-ray detection system using silicon avalanche diodes is proposed. This system will be the basis for a new instrument that will make x-ray diffraction studies faster and more cost efficient.

During Phase I, a new type of detector for x-rays was investigated, and it was successfully demonstrated that monolithic 2-D arrays of detector elements could function as a position-sensitive x-ray detection system. Phase II will continue the device optimization studies begun in Phase I, develop the sensor packaging and electronic circuit for a complete system, and then field test a multielement prototype system. The prototype will demonstrate the advantages of the new detection scheme and will form the basis for the development of a viable commercial product.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Phase I Grants

Title of Project: A Self-Regulating Pump Chamber for Standard Roller Pumps
Principal Investigator: George Repetti
Awardee Organization: Adam Spence Corporation
P.O. Box 1467, Route 34
Wall, NJ 07719
Telephone Number: (201) 681-7070
Awardee Number: 1 R43 HL37188-01A1

The roller pump, used to pump blood flow during cardiopulmonary bypass and to provide long-term circulatory support, is a constant-blood-flow device. It maintains constant flow independently of the clinically expected changes in inlet pressures. A decrease in blood supply to the inlet of the pump without a concomitant decrease in pump speed can cause excessive suction leading to air embolism, thrombosis, and damage by the "venous" cannula to the vessel's intima or, with a bubble oxygenator, the emptying of the oxygenator, pumping air to the patient.

The purpose of this research is to design, fabricate, and evaluate a new, innovative disposable pump chamber for the standard roller pump that self-controls the pump flow as a function of inlet or filling pressure, much like the natural heart. The pump chamber consists of an easily collapsible thin-wall tubing (TWT) housed and sealed in a standard pump tubing. The inner TWT serves to pump blood and the outer tubing serves as a mechanical support and controlled pressure environment for the TWT. This pump chamber can provide additional safety during open heart surgery and also function as an inexpensive, self-controlling mechanism for long-term circulatory support.

Title of Project: Pocket Nebulizer
Principal Investigator: Anatole J. Sipin
Awardee Organization: Anatole J. Sipin Company, Inc.
505 Eighth Avenue, 10th Floor
New York, NY 10018
Telephone Number: (212) 695-5706
Awardee Number: 1 R43 HL40077-01

Beta agonists administered in aerosol form is one of the most potent and widely used bronchodilator therapies. In hospitals, beta agonists are usually administered by compressed air nebulizers. Numerous studies have documented the efficacy of the bronchodilator aerosol delivered from a canister nebulizer, but the major shortcoming of this form of therapy is the poor inhalation technique of some of the patients. Although the technique is relatively simple, many patients fail to learn it correctly.

This proposal is for the development of a miniature pocket-sized nebulizer that is equivalent in aerosol delivery and effectiveness to conventional air-pressure-actuated nebulizers, but has the social acceptability of devices using canister inhalers. Such a nebulizer will be of value to patients who cannot or do not wish to use the canister inhalers, by permitting the aerosol treatment to be performed conveniently, at any time, and without regard to location. It will be especially valuable for infants and young children who cannot use or be taught to use canister-type inhalers.

Title of Project: Composite, Hollow Fiber Membrane Oxygenation Device
Principal Investigator: Don N. Gray, Ph.D.
Awardee Organization: Anatrace, Inc.
1280 Dussel Drive
Maumee, OH 43537
Telephone Number: (419) 891-3030
Awardee Number: 1 R43 HL35989-01A2

The acceptance of extracorporeal oxygenation devices based on gas transfer through a membrane will depend to a large extent on the availability of simpler, easier to use, safer, and lower-cost devices. Oxygenators using microporous hollow fibers have come into wider use the last five years. They present more membrane surface to blood and gas phases for equivalent volume and do not require a supplemental secondary flow for adequate gas transfer. These devices do, however, suffer from the real and potential problems associated with all membrane oxygenators made from microporous materials—possible blood damage due to microbubble intrusion, excessive water transport and seepage, and a lack of selectivity in exchanging oxygen and carbon dioxide.

This proposal suggests an improvement to the present state-of-the-art, microporous-based hollow-fiber oxygenators that eliminates all the above problems by developing a composite permselective/microporous hollow fiber device of optimum geometry and membrane characteristics. The optimized hollow-fiber geometry will be combined with PAS materials that have been shown to have superior permeability to carbon dioxide and oxygen and high biocompatibility with blood.

Title of Project: Glycated Hemoglobin by Automated Affinity Chromatography
Principal Investigator: Melvin H. Keyes, Ph.D.
Awardee Organization: Anatrace, Inc.
1280 Dussel Drive
Maumee, OH 43537
Telephone Number: (419) 891-3030
Awardee Number: 1 R43 HL39342-01

Classical assays for determining blood and urine glucose have limited value for the monitoring of an individual's blood glucose level over time. Measurement of glycated hemoglobin (GHb) is already gaining acceptance for management of persons with diabetes mellitus. GHb levels are not only useful for diagnosis but also for the establishment of care goals and for care reinforcement. In the future, more physicians will use GHb measurements for the routine management of diabetes, and this will require more reliable and cost-effective test methodologies.

Anatrace, Inc. proposes to develop a semi-automated instrument for measurement of GHb that will reduce human error. The heart of the instrument is an affinity support that will possess sufficient ligand side chains and have excellent flow properties. The objective of Phase I is the development of this affinity support.

Title of Project: Mechanism-Based Elastase Inhibitors
Principal Investigator: Clare Biswas, Ph.D.
Awardee Organization: Andrulis Research Corporation
7315 Wisconsin Avenue, Suite 650N
Bethesda, MD 20814
Telephone Number: (301) 657-1700
Awardee Number: 1 R43 HL37843-01

Synthetic elastase inhibitors for use in the treatment of emphysema will be developed. In Phase I, new mechanism-based elastase inhibitors will be synthesized, characterized, and studied as inhibitors of elastase *in vitro*. These inhibition studies will analyze both the reversible behavior of the inhibitors and the time-dependent, irreversible elastase inactivation.

After the chemistry of the elastase inactivation has been elucidated in Phase I, a structure-activity study will be carried out in Phase II to develop the most potent elastase inhibitors. Because the absence of natural elastase inhibitors in the lung is believed to be responsible for much of the pathogenesis observed in emphysema, these new synthetic elastase inhibitors should be very valuable for use in replacement therapy for patients with emphysema.

Title of Project: NADH Fluorescence Imaging in the Heart
Principal Investigator: Clyde H. Barlow, Ph.D.
Awardee Organization: Barlow Scientific
6307 Tamoshan Drive, Northwest
Olympia, WA 98502
Telephone Number: (206) 866-1244
Awardee Number: 1 R43 HL37798-01A1

The long-term goal of this research is to develop quantitative imaging methods for tissue bioenergetic studies. Toward this end, it is proposed to construct and evaluate an instrument that will image the response of mitochondrial metabolites to ischemia and hypoxia in rabbit hearts *in situ*. Instrument operation is based on fluorescence emission from mitochondrial NADH in heart epicardium. These changes can be measured fluorometrically and will be imaged at the surface of perfused and *in situ* rabbit hearts.

In Phase I, a video fluorometer will be constructed from a low-light-level video camera, frame grabber, and computer. Alterations in regional NADH concentrations will be analyzed from multiwavelength fluorescence and/or reflectance images. Procedures for compensating fluorescence emission for internal absorption due to blood volume changes will be developed to generate quantitative fluorescence images. The efficiency of the compensation will be tested with rabbit hearts *in situ* during procedures involving local ischemia or hypoxia. Proof of feasibility in Phase I will allow the range of fluorochromes to be expanded in Phase II to include pH, metal ion, and membrane-potential-sensitive dyes. The instrument will be of value for a wide range of investigators who require information concerning regional metabolic alterations in tissues or organs.

Title of Project: Computerized Telephone-Based Smoking Cessation System
Principal Investigator: Sid J. Schneider, Ph.D.
Awardee Organization: Behavioral Health Systems, Inc.
200 Main Street
Ossining, NY 10562
Telephone Number: (914) 762-6098
Awardee Number: 1 R43 HL38555-01

The present proposal is to develop and evaluate a system for treating the large number of smokers who wish to quit smoking, feel unable to quit on their own, but still refuse to attend face-to-face smoking cessation programs. The system combines technologies developed by Behavioral Health Systems, Inc. (BHS) and Computers in Psychiatry/Psychology, Inc. (CPP). BHS has developed a software and computer conferencing system that helps smokers, seated at a computer terminal, to formulate and carry out an individualized smoking cessation plan. CPP has developed an automated, interactive telephone system that uses voice synthesis and recognition, and automatic dialing and answering to communicate with people participating in health promotion programs. By putting the contents of the BHS program on the CPP telephone system,

BHS can offer a powerful, personalized smoking cessation program to any smoker with an available telephone for as many months as the smoker wishes to participate. A very large group could be treated using a minimum of professional time.

The effectiveness of the system in getting smokers to participate, and then to quit smoking, will be compared with the effectiveness of a traditional smoking cessation approach. The convenience, affordability, privacy, and effectiveness of the proposed system may make it a useful tool for treating a number of behavioral disorders.

Title of Project: Coraflex Polyurethane Prosthetic Valve Program
Principal Investigator: David L. Purdy
Awardee Organization: Biocontrol Technology, Inc.
300 Indian Springs Road
Indiana, PA 15701
Telephone Number: (412) 349-1811
Awardee Number: 1 R43 HL36481-01A2

Although prosthetic heart valves have been in clinical use since 1960, a need exists for a valve that does not require anticoagulants and has a long life expectancy. Biocontrol Technology, Inc. has developed a valve that promises to meet these criteria. It resembles the human aortic valve, or the porcine or bovine valves, but it is made of biocompatible, fatigue-resistant Coraflex polyurethane. The valve is designed to have minimal membrane stress, shear strength, and subsequent hemolysis. The valve has been tested in a cardiac-pulse duplicator and in dogs and has demonstrated flow characteristics similar to porcine valves, which do not require anticoagulants.

In addition, to prevent valve calcification, the prosthesis will contain the anticalcification agent, ethanehydroxydiphosphonate (EHDP), in a slow-release form (>30 years extrapolated drug delivery) as part of both the leaflet structure and the support ring.

Phase 1 of the research program will consist of continued fatigue testing of the Coraflex valve on a specially designed heart-valve-fatigue test system. It provides dynamic pressure characteristics similar to those experienced in the actual operating environment. Phase 1 will also involve *in vitro* studies of EHDP controlled-release drug delivery from the prosthesis. The successful completion of fatigue testing and formulation of a suitable EHDP controlled-release drug delivery system in Phase I would lead to complete performance and animal tests in Phase II, in preparation for clinical trials.

Title of Project: Heparin Adsorption Complexes for Blood Compatibility
Principal Investigator: Donald E. Gregonis, Ph.D.
Awardee Organization: Biomaterials International, Inc.
420 Chipeta Way, Suite 180
Salt Lake City, UT 84108
Telephone Number: (801) 583-8444
Awardee Number: 1 R43 HL37857-01

The anticoagulant, heparin, will be derivatized with biologically compatible hydrophobic macromolecules to make them water insoluble. This derivatization will occur through hydrophilic spacer groups, allowing the heparin to extend into the aqueous environment and retain its bioactive configuration. These heparin derivatives will be solvent-coated onto biomedical devices to provide low-cost, immobilized heparin surfaces applicable to essentially all types of polymers used for catheters, tubing, membrane oxygenators, etc. This Phase I proposal addresses the heparin derivatization, adsorption stability, toxicity, and biological effectiveness of the adsorption complexes on surfaces.

Long-term goals in Phase II include specifically tailoring high molecular weight molecules to bind to heparin so that fewer molecules would

need to be bound to immobilize heparin to the surface. Radiolabeled experiments will be done to verify that no modified heparin molecules will desorb in the blood environment. *In vivo* animal studies will be done to show the effectiveness of the immobilized heparin in both acute and long-term applications.

Title of Project: Development of an Improved Small-Diameter Vascular Graft
Principal Investigator: Paul T. Picciano, Ph.D.
Awardee Organization: BioPolymers, Inc.
309 Farmington Avenue
Farmington, CT 06032
Telephone Number: (203) 674-1444
Awardee Number: 1 R43 HL38567-01

For over 30 years, a major goal of vascular surgery has been to improve bypass surgery through the development of an ideal prosthetic graft. Although saphenous vein is the preferred substrate for occluded small-to-medium veins, frequently it is unavailable or unsuitable for a great number of patients who need this surgery. Two of the problems that have impaired the development of such a graft are poor cell attachment to seeding grafts and poor retention of cells by grafts when exposed to *in vitro* and *in vivo* flow conditions. Although the use of fibronectin has resulted in some improvements with respect to these parameters, development of grafts is still far from complete.

This research will involve experiments on mussel adhesive protein (MAP), which has the potential to increase the adhesion of cells to grafts *in vitro* and *in vivo*. MAP has been found to be effective as a cell-attachment factor *in vitro* and is biocompatible with cells and tissues. Experiments are designed to explore attachment efficiency of cells to grafts and the retention of these cells by grafts during perfusion.

Title of Project: Therapy for Thalassemia
Principal Investigator: Donald H.J. Mackay, Ph.D.
Awardee Organization: Biosym Technologies, Inc.
9605 Scranton Road, Suite 101
San Diego, CA 92121
Telephone Number: (619) 458-9990
Awardee Number: 1 R43 HL38563-01

The overall objective of this proposed project is to extend receptor-based drug design to include the use of modern, state-of-the-art simulation of the structure, energetics, and dynamics of protein-protein and protein-ligand interactions. In particular, Biosym Technologies, Inc. proposes to use these techniques to model an alpha-hemoglobin tetramer and to use information obtained from these studies for designing ligands that stabilize such oxygen carrier alpha-tetramers. The resulting ligands could ultimately be used in the treatment of beta thalassemia.

Title of Project: Portable System for Control of Anticoagulant Therapy
Principal Investigator: Bruce J. Oberhardt, Ph.D.
Awardee Organization: BIOTHERM, Inc.
P.O. Box 13417
Research Triangle Park, NC 27709
Telephone Number: (919) 544-2952
Awardee Number: 1 R43 HL37174-01A1

BIOTHERM Inc. proposes to design and develop a portable system, analogous to a hand-held glucose meter, to permit rapid, convenient blood coagulation testing on freshly drawn samples from patients undergoing anticoagulant therapy. This cost-effective system would better help meet the needs of patients and provide for earlier release from hospitals. The use of such a system in the physician's office, in a free-standing ambulatory care facility, and in the home offers the potential for more rapid test turnaround time and consequently better control of therapy in patients with thromboembolic problems. During Phase I, a prototype reagent system together with an electronic measurement device will be fabricated, tested, and analyzed for feasibility. The system will be based on a sensitive coagulation monitoring technique.

Title of Project: Angiogenesis with Antagonist and Agonist Analogs of Basic FGF
Principal Investigator: Andrew A. Protter, Ph.D.
Awardee Organization: California Biotechnology, Inc.
2450 Bayshore Parkway
Mountain View, CA 94043
Telephone Number: (415) 966-1550
Awardee Number: 1 R43 HL39348-01

Basic Fibroblast Growth Factor (bFGF) is a potent mitogen and angiogenesis-promoting factor. Analogs of bFGF will be synthesized by *in vitro* mutagenesis of a DNA fragment coding for human bFGF. The mutated bFGF-coding DNA fragment will be engineered into a bacterial expression vector and transfected into bacteria. The bFGF analogs produced by the bacteria will be purified by heparin-sepharose chromatography and tested for agonist and antagonist activity to bovine pituitary bFGF using two different cell assays and a bFGF-receptor-binding assay. This is a first step toward developing potential therapeutics for regulating angiogenesis based on the structure of bFGF.

Title of Project: Formulation of Recombinant Human Lung Surfactant
Principal Investigator: R. Tyler White, Ph.D.
Awardee Organization: California Biotechnology, Inc.
2450 Bayshore Frontage Road
Mountain View, CA 94043
Telephone Number: (415) 966-1550
Awardee Number: 1 R43 HL37801-01

The objective of the proposed research is formulation of an effective synthetic surfactant to be used in treatment of infant Respiratory Distress Syndrome (RDS). RDS is caused by inadequate levels of lung surfactant at birth, and is presently treated by assisting the newborn with mechanical respiration, a therapy available only at a limited number of medical centers, and one which can severely damage the lungs.

Treatment of RDS using natural lung surfactant supplements appears to be effective, but is strictly limited by the scarcity of human surfactant proteins, which in addition to phospholipids, are key components of surfactant. The application of recombinant DNA techniques to isolate and express the genes for the human surfactant proteins should provide unlimited quantities of synthetic surfactant, formulated with recombinant proteins and pure phospholipids. One of the two major surfactant proteins (SP28-36) has already been cloned and expressed by recombinant DNA methods. California Biotechnology, Inc. proposes to isolate and express the gene for the remaining human surfactant protein, SP17.

Title of Project: Purification of an Autocrine Angiogenesis Inhibitor
Principal Investigator: Mark A. Snyder, Ph.D.
Awardee Organization: California Biotechnology, Inc.
2450 Bayshore Frontage Road
Mountain View, CA 94043
Telephone Number: (415) 966-1550
Awardee Number: 1 R43 HL37806-01

A protein has been identified from a cultured cell line which inhibits the growth of capillary endothelial cells *in vitro*. This protein will be purified from conditioned growth medium and used in *in vitro* and *in vivo* model systems to test its ability to inhibit the formation of new capillaries. This is the first step toward developing a therapy that will be used in the treatment of solid tumors, various retinopathies, psoriasis, arterial occlusive disease, and in birth control, all of which involve either neovascularization or growth of endothelial cells themselves.

Title of Project: Blood Bank Immunodiagnostics for Platelet Proteins
Principal Investigator: David H. Bing, Ph.D.
Awardee Organization: CBR Laboratories, Inc.
800 Huntington Avenue
Boston, MA 02115
Telephone Number: (617) 741-6470
Awardee Number: 1 R43 HL39338-01

During the next year, over 4 million units of platelets will be transfused in the United States for a variety of medical reasons. In spite of the remarkable body of knowledge about platelet physiology and biochemistry, efficacy of this blood product in correcting bleeding problems is usually measured according to the platelet count and the bleeding time, both of which can be determined only after the platelets have been transfused. Poor *in vivo* efficacy and survival correlate with the extent to which the platelets have been activated prior to transfusion.

Within the past few years, a number of novel platelet proteins have been described, which are found only on the surface of activated platelets. One such protein, the PADGEM or GMP-140 protein, is found in the alpha granules but is expressed on the surface of the platelet after this cell has been activated to express its biochemical potential in hemostasis. CBR Laboratories, Inc. proposes to develop a rapid immunodiagnostic test for platelet activation that will measure PADGEM/GMP-140 on the surface of platelets during the time these cells are stored prior to transfusion.

In this Phase I study, CBR Laboratories, Inc. will determine whether the kinetics of appearance of this protein on the platelet surface during storage correlates with the presence of known biochemical markers of platelet activation and the *in vivo* survival of this cell. If correlation is found between these two factors, in Phase II, CBR Laboratories, Inc. will format a suitable immunoassay for PADGEM/GMP-140 on platelet surfaces for use in the blood bank and undertake full clinical trials in humans.

Title of Project: Pure Factor IX for Treatment of Hemophilia B
Principal Investigator: David H. Bing, Ph.D.
Awardee Organization: CBR Laboratories, Inc.
800 Huntington Avenue
Boston, MA 02115
Telephone Number: (617) 741-6470
Awardee Number: 1 R43 HL39335-01

National Institutes of Health
National Heart, Lung, and Blood Institute

Hemophilia B is a severe bleeding disorder characterized by a functional deficiency in the blood coagulation protein factor IX (or Christmas factor). Therapy for bleeding episodes in these patients requires the intravenous replacement of factor IX given as fresh frozen plasma or with commercially available concentrates of factor IX in which the protein is only partially purified. Although these commercial materials have proven to be effective in treating this disease, they contain many impurities, are often contaminated with a virus, and are associated with significant morbidity.

The goal of this project is the development of a highly purified form of factor IX. Factor IX will be obtained by using a recently described invention that employs conformation-specific antibodies against human factor IX to purify this protein. This factor IX will be homogeneous and thus suitable for intravenous therapy. Published studies of factor IX purified by this methodology indicate that it is free of the contaminants and infectious agents responsible for complications associated with the currently commercially available concentrates. In this Phase I study, sufficient factor IX will be purified to accomplish studies of acute toxicity in rabbits and the ability to correct the bleeding deficiency in hemophiliac dogs.

Title of Project: Cryopreservation of Venous and Arterial Tissue
Principal Investigator: Robert T. McNally, Ph.D.
Awardee Organization: CryoLife, Inc.
2211 New Market Parkway, Suite 142
Marietta, GA 30067
Telephone Number: (404) 952-1660
Awardee Number: 1 R43 HL37789-01

Currently in the United States there are 360,000 small vessel implants and 100,000 peripheral vascular reconstructions annually. Of this population needing vascular surgery, approximately 15 percent of the patients do not have vessels suitable for autografts. A prototype procedure has been developed for the cryogenic preservation of arteries and veins with an intact endothelial lining for transplantation. This proposal is for completion of the development of cryogenic technology along with ancillary surgical and transport methodologies to enable the commercialization of arterial and venous homografts for the medical community.

In Phase I, optimization of the cryobiological procedures and testing of the efficacy of vessels stored using this technology will be performed in a canine model system. Efficacy of the preservation will be judged by the integrity of the endothelium using morphological criteria, patency, factor VIII staining, adhesion of radio-labeled platelets, *in vitro* proliferative capacity, and prostacyclin production.

Title of Project: A Portable Psychophysiology Lab for Stress Assessment
Principal Investigator: Lyle H. Miller, Ph.D.
Awardee Organization: Davicon, Inc.
54 Sun Street
Waltham, MA 02154
Telephone Number: (617) 738-4814
Awardee Number: 1 R43 HL37102-01

Traditional psychophysiological stress research has been limited to the laboratory because of the nature of the necessary equipment. The real-world validity of such research is questionable, making epidemiological field studies necessary if such data are to be used effectively in developing improved diagnostic and preventive intervention procedures. The lack of a truly portable psychophysiology microlaboratory appears to be the major impediment to conducting these important field studies.

The ideal "microlab" would be a fully computerized, energy-efficient, truly portable version of the traditional psychophysiology laboratory. This

means that such a microlab would be capable of stimulus generation, measurement of multiple parameters of psychophysiological reactivity to stress, stress reduction, psychophysiological data, and transmission of digitized data to mainframe computers in file-compatible formats.

The proposed research is to determine the feasibility of developing such a microlab for use in field studies of psychophysiological reactivity to stress.

Title of Project: Protective Treatment for Catheters
Principal Investigator: John B. Newkirk, D.Sc.
Awardee Organization: Denver Surgical Developments, Inc.
6851 Highway 73
Evergreen, CO 80439
Telephone Number: (303) 674-5294
Awardee Number: 1 R43 HL37184-01A1

The long-term objective of this research is to make commercially available central venous catheters (CVC) that have been chemically treated to reduce their tendency to induce infections, thereby bringing major humanitarian benefits and substantial reductions in hospital care costs.

Specifically, Denver Surgical Developments, Inc. will: (1) apply an already developed process for antimicrobial protection of silicone rubber to a commonly used CVC (Hickman) device; (2) determine the duration and levels of antimicrobial activity of optimally treated catheters during perfusion with saline, nutritional, and oncotherapeutic solutions; (3) determine the degrees of protection of treated catheters against lumen colonization *in vitro*; (4) determine the biocompatibility in mouse tissue of the treated catheter material; and (5) determine the effects of normal storage on antibacterial activity and tensile strength of treated catheters.

Title of Project: Decontamination of Platelet Concentrates
Principal Investigator: Gary P. Wiesehahn, Ph.D.
Awardee Organization: Diamond Scientific Company
2538 Southeast 43rd Street
Des Moines, IA 50317
Telephone Number: (515) 262-9341
Awardee Number: 1 R43 HL39378-01

The overall objective of the research is to define a system for decontaminating platelet concentrates. Present screening of donated blood does not detect all potentially infectious contaminants. Therefore, it is important to find a means of rendering blood products nonspecifically noninfectious to reduce the risk of viral infection and bacterial sepsis associated with therapeutic use of platelet concentrates.

Diamond Scientific Company proposes to demonstrate the ability to inactivate an animal-virus model in platelet concentrates. The effects of the inactivation treatment on the following will be examined: (1) gross platelet morphology, by measuring platelet count as a function of inactivation time; (2) response of platelets to aggregating agents; and (3) platelet activation by fluorescent antibody assay.

This research has the potential to be commercially useful in safeguarding the estimated 5 to 7 million units of platelets transfused annually.

Title of Project: Identification and Isolation of the Cystic Fibrosis Gene
Principal Investigator: Kirk E. Fry, Ph.D.
Awardee Organization: Genelabs, Inc.
871 Industrial Road, Building J
San Carlos, CA 94070
Telephone Number: (415) 594-1600
Awardee Number: 1 R43 HL39354-01

Complete and partial restriction-enzyme digests of genomic DNA will be analyzed by PFGE to map the known DNA markers linked to the gene for cystic fibrosis. These techniques will be used to identify large DNA fragments that span the chromosomal site of the cystic fibrosis gene. These fragments will be used to prepare cDNA libraries corresponding to all mRNAs encoded by DNA of the size of the fragment.

Further screening of the cDNA libraries will be performed to isolate those clones that are encoded on chromosome 7. Each such clone from cystic fibrosis, normal pancreatic, and nasal polyp tissue will be compared. Potential mutations will be identified, and DNA from a group of diseased subjects and phenotypically normal individuals will be evaluated to confirm the association of the mutation with the disease.

Title of Project: Cardiac Tracer Scans Using X-Ray-Induced Fluorescence
Principal Investigator: Graham V. Walford, Ph.D.
Awardee Organization: GNL Associates, Inc.
20 Argonne Plaza, Suite 290
Oak Ridge, TN 37830
Telephone Number: (615) 482-3149
Awardee Number: 1 R43 HL37786-01A1

Some of the most important techniques for the detection of heart disease involve the use of radioactive tracers. These tracers yield information on cardiac chamber volumes, cardiac output, ejection fractions, regional perfusion patterns, and zones of frank tissue damage. GNL Associates, Inc. proposes to develop an alternative tracer technology that does not require the injection of radionuclides into the circulatory system, but rather is based upon an x-ray-induced fluorescence of iodine present in commonly used radiographic contrast agents.

These iodine concentrations will be tracked with a new type of radiation-detection system that has high resolution in both space and energy. The two-way high resolution is achieved with a dual solid-state detector system consisting of an ion-implanted, resistive, silicon detector (high spatial resolution) and an ultrapure germanium detector (high energy resolution). By using off-the-shelf technology in a new way, it is expected that this system can be developed at a considerably lower cost than current radioisotope scanning systems. Such a device also has the commercial potential for nonmedical uses.

Title of Project: Aluminum Removal by Chelators Immobilized in Hollow Fiber
Principal Investigator: Clara M. Ambrus, M.D., Ph.D.
Awardee Organization: Hemex, Inc.
143 Windsor Avenue
Buffalo, NY 14209
Telephone Number: (716) 883-8382
Awardee Number: 1 R43 HL37821-01A1

Hemex, Inc. has developed a hollow fiber device with immobilized chelators for the extracorporeal removal of toxic metals from blood, specifically aluminum (Al). This device, similar to a hemodialysis cartridge, is a novel approach to detoxification, with unique advantages over existing treatments: (1) the immobilized chelator does not enter the blood, minimizing the danger of toxicity; (2) the device functions with efficiency due to the large concentration of chelator and extensive contact area and is specific toward a given metal according to the chelator used; and (3) blood compatibility of the hollow fibers assures safety of application. The safety and efficacy of the proposed device are particularly attractive as the current chelator therapy of Al intoxication has potential toxicity.

In Phase I, Hemex, Inc. plans to finalize design of the device by selecting specific chelators for Al and testing their efficacy *in vitro*, using blood from patients with Al intoxication. The most effective device will be further evaluated in Phase II in experimental animals to assure *in vivo* efficacy and safety. The development of the optimal device will lead to an Investigational Device Exemption (IDE) and clinical testing in patients on chronic hemodialysis.

Title of Project: Fluoride Glass Fiber for Infrared Laser Power Delivery
Principal Investigator: Dank Tran
Awardee Organization: Infrared Fiber Systems, Inc.
2301-A Broadbirch Drive
Silver Spring, MD 20904
Telephone Number: (301) 622-9546
Awardee Number: 1 R43 HL39466-01

This project is intended to result in an infrared fiber laser catheter for use in laser angioplasty, ophthalmic surgery, neurosurgery, and endoscopic microsurgery where precision of tissue removal is a necessity. The fiber will be made from zirconium fluoride glass, which has very low loss at 2.9 microns, the wavelength of maximum tissue absorption. Improvements will be made in the fiber strength, chemical durability, and laser damage threshold. This will be done by developing improved glass-processing techniques based on Infrared Fiber Systems, Inc.'s experience in working with heavy metal fluoride glass and developing waterproof coatings to provide chemical durability. The resulting fiber will be usable with a pulsed Er:Yag laser.

Title of Project: Single Optical Fiber Probe for pH/pO_2/pCO_2 Detection
Principal Investigator: Robert A. Gutcheck, Ph.D.
Awardee Organization: International Biomedics, Inc.
1631 220th, South East
Bothell, WA 98021
Telephone Number: (206) 485-2200
Awardee Number: 1 R43 HL37824-01

Present catheter-based optical probes (optrodes) for continuous monitoring of various parameters in body fluids require separate sensors and fibers for each parameter measured, thus requiring large delivery devices. A small, inexpensive, disposable, and continuously monitoring multiparameter probe would be cost effective, present clinical information immediately, and provide diagnostics not presently available. The objective is to demonstrate the feasibility of a compound sensor optrode, in which multiple parameters (pH, pCO_2, pO_2) can be monitored by a single, small, optical fiber.

The specific aims of Phase I are to first build a pCO_2/pO_2 and then an O_2/pH sensor on a single optical fiber and measure the effectiveness of the probe in body fluids with known O_2/CO_2 concentrations. The next step will be to devise a method for combining all three sensors on the same optical fiber.

The Phase II objective will be to build and characterize a single optical fiber, multisensing probe that can fit inside a 22-gauge catheter, yet allow sufficient blood draw and blood pressure-monitoring performance.

Title of Project: Immunosorbent Device for LDL Removal from Whole Blood
Principal Investigator: Laura H. Silberstein, Ph.D.
Awardee Organization: Invitron Corporation
4649 Le Bourget
St. Louis, MO 63134
Telephone Number: (314) 426-5000
Awardee Number: 1 R43 HL37913-01

High blood levels of LDL have been established as causative for atherosclerosis and coronary heart disease. For selected patients, extracorporeal LDL removal is the most effective therapy. The goal of this project is to develop a monoclonal antibody-based immunoadsorption device capable of removing low-density lipoprotein (LDL) from hypercholesterolemic whole blood circulated in a low-pressure extracorporeal venous shunt.

Phase I will extend previous studies demonstrating safety and efficacy of goat polyclonal antibody-based immunosorbents for removal of LDL from whole blood *in vitro* to the extracorporeal removal of LDL from whole blood of experimental animals. In addition, mouse anti-LDL monoclonal antibodies will be tested for their suitability in the LDL-immunosorbent device. Methods of chemical sterilization, immunosorbent regeneration, and storage between uses will also be studied.

During Phase II, advanced membrane technology, sorbent configuration, and coupling chemistry will be evaluated for improved immunosorbent efficacy and capacity. Extended human trials will begin with the identification of a safe and efficacious LDL-immunosorbent device prototype. During the course of these studies, new technology will be developed in three areas: (1) design of whole-blood immunosorbents, (2) sterilization of immunosorbents, and (3) application of monoclonal antibodies to clinical immunosorbents.

Title of Project: Intravascular Grafting Device
Principal Investigator: Harrison M. Lazarus, M.D.
Awardee Organization: Lazarus Medical, Inc.
324 Tenth Avenue, Suite 260
Salt Lake City, UT 84103
Telephone Number: (801) 322-4406
Awardee Number: 1 R43 HL36508-01A2

This research will continue the development of a new device to facilitate the replacement of aortic aneurysms. The device for performing the grafting will be introduced from a peripheral arterial site, so that the major body cavities (chest and abdomen) will not be entered for grafting purposes, thus decreasing the morbidity and mortality associated with these procedures. The grafting and replacement of the aneurysmal portion of the aorta will take place within the existing vessel. With the rapid increase of the older age group in the U.S. population, the problem of aortic aneurysms will also increase. The availability of such an intravascular grafting device could revolutionize the way aortic aneurysms are treated. Commercial application is readily apparent as 100,000 aortic surgical procedures are performed annually.

Phase I funds would assure the completion of the design and testing of the intravascular grafting device. During Phase II, the device will be submitted to the Food and Drug Administration (FDA) for approval to do human testing. Subsequent FDA approval will be sought for use of the device to replace thoracic aortic aneurysms.

Title of Project: Computer Simulation for Teaching Cardiology Trainees
Principal Investigator: Nils S. Peterson
Awardee Organization: Learning Tools
1220 Monmouth Street, #34
Independence, OR 97351
Telephone Number: (503) 838-1839
Awardee Number: 1 R43 HL37790-01

The cardiovascular system is an integrated system where the performance of each part of the system depends on the characteristics of all other parts of the system. However, the functions of the components of the cardiovascular system are taught individually. For example, cardiac performance may be presented in terms of dp/dt, ejection fraction, or function curves, while vascular beds are studied in terms of compliance or steady-state resistance. Often, students cannot easily reconcile these representations into a whole system understanding.

A mathematical model has been developed that characterizes the chambers of the heart and the vascular beds in terms of instantaneous pressures, volumes, and flows. This approach has been used to develop computer simulations for teaching medical physiology. These tools have been found to improve student understanding of the cardiovascular system. However, these prototypes are not complete enough or easy enough for a physician to use as a cardiology teaching tool.

Learning Tools will develop a computer simulation for teaching cardiology that has (1) simulations of the isolated left heart and the integrated cardiovascular system; (2) an environment for recreating the natural history of diseases; and (3) a practice environment where students diagnose cardiovascular problems.

Title of Project: Development of New Anti-Platelet Aggregating Agents
Principal Investigator: Barry Sears
Awardee Organization: Lipid Specialties, Inc.
21 Tioga Way
Marblehead, MA 01945
Telephone Number: (617) 639-2400
Awardee Number: 1 R43 HL38574-01

Platelet aggregation plays a major role in cardiovascular disease. Much of the present pharmaceutical research is focused on inhibitors of the formation of thromboxane A_2, a prostaglandin derived from arachidonic acid. The dietary intake of an essential fatty acid, eicosapentaenoic acid (EPA), has been shown to decrease thromboxane A_2. Also, other essential fatty acids, gamma linolenic acid (GLA) and dihomo gamma linolenic acid (DGLA), have been shown to decrease platelet aggregation by a different mechanism: the increase in the plasma levels of PGE_1. The goal of this research is to prepare a pharmaceutical-grade edible oil containing GLA that can be tested in clinical trials for its ability to reduce platelet aggregation. The rare seed source that has the highest concentration of GLA also contains a potentially toxic alkaloid. The successful completion of Phase I will be to demonstrate that a pharmaceutical-grade oil can be produced that is also devoid of the toxic alkaloid. If Phase I is successful, then Phase II will focus on clinical trials with such a GLA-containing edible oil to investigate the reduction of platelet aggregation.

Title of Project: New Therapeutic Agents to Reduce Triglyceride Levels
Principal Investigator: Barry Sears
Awardee Organization: Lipid Specialities, Inc.
21 Tioga Way
Marblehead, MA 01945
Telephone Number: (617) 639-2400
Awardee Number: 1 R43 HL38592-01

High triglyceride levels have been shown to be a risk factor in cardiovascular disease. The high-dose dietary intake of marine oils containing an essential fatty acid, eicosapentaenoic acid (EPA), has been shown to be very effective in reducing triglyceride levels in both Type V hyperlipidemics and normals. However, the dietary intake of large amounts of marine oils also means that high levels of cholesterol are also being ingested. The goal of this research is to develop a methodology for producing a pharmaceutical grade of marine oil rich in EPA, but low in cholesterol. Lipid Specialities, Inc. will investigate and compare two techniques: supercritical fluid extraction and molecular distillation. The EPA-containing oils prepared using each technique will be analyzed by a number of tests standard in the edible oil industry to determine whether the finished product has the technical specifications to be considered a pharmaceutical-grade material. If Phase I is successful, then Phase II studies will focus on using these low-cholesterol oils in clinical trials.

Title of Project: Omega-3 Polyunsaturated Fatty Acids from Algae
Principal Investigator: David J. Kyle, Ph.D.
Awardee Organization: Martek Corporation
9115 Guilford Road
Columbia, MD 21046
Telephone Number: (301) 490-2566
Awardee Number: 1 R43 HL38547-01

Recent investigations indicate a significant correlation between dietary supplements of polyunsaturated fatty acids (PUFA), especially omega-3 PUFAs, and reduced incidence of coronary heart disease. Clinical interests have focused on potential usage of omega-3 PUFAs, in the treatment of hypercholesteremia and hypertriglyceridemia. At present, the only source of omega-3 PUFAs is oil from certain marine fishes. However, many species of algae also produce large amounts of omega-3 PUFAs and Martek Corporation believes that this group of organisms could provide an invaluable supply source of omega-3 PUFAs for clinical trials and/or food additive testing using algal monoculture. Phase I will involve (1) establishing several omega-3 PUFA-producing algal species in culture; (2) optimizing the growth conditions and determining the maximum omega-3 PUFA productivities; and (3) extracting and purifying the omega-3 PUFA's in preparative quantities.

If significant advantages over the fish oil source are identified, Phase II will involve scale-up production and an effort targeted to increase specific omega-3 PUFA outputs from algal sources by strain improvement and genetic modification.

Title of Project: A Noninvasive Cardiopulmonary Anesthesia Monitor
Principal Investigator: Ingvar E. Sodal
Awardee Organization: Masstron, Inc.
5710 Flatiron Parkway
Boulder, CO 80301
Telephone Number: (303) 440-7227
Awardee Number: 1 R43 HL37839-01A1

During most surgical procedures the patient is paralyzed and must depend completely on the anesthesiologist to maintain such vital physiologic functions as breathing and heart rate. It is therefore not surprising that, with relatively few effective physiological monitors available to the anesthesiologist, the frequency of mishaps during surgery is high. Of the approximately 20 million surgical procedures performed annually in this country, it is estimated that about 6,000 people die or become seriously disabled as a result of the anesthetic procedure.

Anesthesia monitoring can be divided into (1) monitors that primarily check the performance of the anesthesia delivery system, and (2) monitors that measure the physiological effects of the anesthetic procedure on the patient. The goal of the proposed work is to extend the capabilities of a monitoring system presently designed for performance checking to also monitor physiological variables. The proposed system will be capable of continuously monitoring circulation, ventilation, and gas exchange variables. Anesthetic gas uptake and tissue concentration are by-product measurements of the method.

The key to economical and high-quality measurements of these cardiopulmonary parameters is the development of a miniaturized, high-quality mass spectrometer, already competitively priced for service as just an anesthetic gas monitor. However, as this analyzer represents the major cost of a total anesthesia/physiologic monitoring system, the physiological monitoring capability represents an additional, substantial monitoring benefit at a disproportionately modest cost.

Title of Project: Noninvasive Detection of Microemboli
Principal Investigator: Justin S. Clark, Ph.D.
Awardee Organization: Masstron, Inc.
5757 Central Avenue
Boulder, CO 80301
Telephone Number: (303) 440-7227
Awardee Number: 1 R43 HL37157-01

Because present methods for detection of pulmonary emboli utilize imaging techniques, the size of emboli detectable by these methods is limited by the inherent spatial resolution of x-ray and gamma cameras. Microemboli (clots of the microcirculation) are therefore too small to be detected by standard methods. Because microemboli are not detectable, there is no direct evidence that microemboli involvement is of clinical significance. However, microembolic involvement has been proposed as a principal causative factor in Adult Respiratory Distress Syndrome (ARDS), a trauma-associated disease having a high mortality (over 50 percent) in young adults. Microembolic involvement in other trauma-associated conditions, including surgery, is also speculative.

The purpose of this proposal is to establish the feasibility of applying a new and noninvasive method to the development of a practical instrument for sensitive and quantitative detection of microembolic involvement in human lungs. Phase I will address validation of the principle of the new method in experimental animals. The economic goal of Phase II will be to test the likelihood of microembolic detection becoming a standard medical practice. Accomplishment of this goal will involve a combination of technical development and scientific studies. Given a successful Phase I, Phase II will (1) develop a practical instrument for human studies, and (2) perform clinical research studies designed to verify the microembolic involvement in ARDS and other trauma-associated conditions.

Title of Project: Biologically Stable Heparin Derivatives
Principal Investigator: Daisy S. McCann, Ph.D.
Awardee Organization: McCann Associates, Inc.
3139 South Wayne Road
Wayne, MI 48148
Telephone Number: (313) 721-0300
Awardee Number: 1 R43 HL38604-01

A series of covalent heparin-protein complexes with prolonged *in vivo* half-lives of the heparin moiety and high anticoagulant activity will be developed. A series of proteins covering a broad range of molecular weights and isoelectric points will be chosen for these conjugates. Various conjugation techniques will be investigated to determine the method that will retain the best anticoagulant activity for the heparin. The relative ability of the covalent protein-heparin complexes to catalytically accelerate the inhibition of thrombin and factor X will be measured by stopped-flow fluorimetry. Prolongation of activated partial thromboplastin time will be used to evaluate potential *in vivo* anticoagulant activity. Ultimately, but not as part of the Phase I studies, half-lives and efficacy will be determined in controlled clinical studies.

Title of Project: Sensors for Control/Monitoring of Therapeutic Deep Heat
Principal Investigator: Lawrence E. Larsen, M.D.
Awardee Organization: Medical Microwave Research Corporation
808 Pershing Drive, Suite 104
Silver Spring, MD 20910
Telephone Number: (301) 585-0464
Awardee Number: 1 R43 HL37198-01A1

The desired response for therapeutic deep heat in the musculoskeletal system is not simple temperature elevation. Rather, Medical Microwave Research Corp. proposes a physiological endpoint for determination of therapeutic response. The therapeutic response will be measured noninvasively with an electromagnetic sensor which will operate with any source of therapeutic deep heat such as ultrasound or diathermy. Phase I will use the latter. The deep heating will be supplied by a previously developed, proprietary, contracting applicator operating at 918 MHz at a maximum muscle SAR of 150-200 mW/g for 20 minutes in normal human volunteers. Since the proposed noninvasive sensor can be retrofitted to any form of deep heating, it is applicable to existing as well as new equipment for therapeutic deep heating.

Title of Project: Microwave Device for Blood Warming and Temperature Control
Principal Investigator: Richard S. Grabowy
Awardee Organization: Microwave Medical Systems, Inc.
52 South Avenue, M/S-704
Burlington, MA 01803
Telephone Number: (617) 272-3000
Awardee Number: 1 R43 HL38564-01

It is estimated that almost 75,000 persons will die each year of acute respiratory insufficiency caused by lung disease. To address this problem, extracorporeal membrane oxygenation (ECMO) is used to provide external pumping and membrane oxygenation to assist the weakened or failing heart. Heat exchangers in the extracorporeal circulation (ECC) path are necessary to prevent water loss associated with evaporative heat loss in long-term ECMO. Here, a short path length is particularly desirable to minimize trauma to blood components coming in contact with foreign surfaces.

Heat exchangers can also be used to solve the problem of hypothermia and its associated coagulopathy occurring with trauma, the leading cause of death in young Americans. A small, portable unit used in the line where blood and fluid are given could be used as early as the prehospital phase of support to prevent hypothermia.

A microwave transmitter (heater) system is proposed to address problems associated with long-term blood warming for ECMO and short-term, rapid warming for trauma. This system would be small, portable, and provide for a short ECC path. In addition, a closed-loop temperature control system is possible by combining a passive, noninvasive, microwave thermometry system with the transmitter.

Title of Project: Development of a Stable Ultrasound Contrast Agent
Principal Investigator: Kenneth J. Widder. M.D.
Awardee Organization: Molecular Biosystems, Inc.
11180-A Roselle Street
San Diego, CA 92121
Telephone Number: (619) 452-0681
Awardee Number: 1 R43 HL39364-01

Until recently, cardiac ultrasound has offered no method of evaluating myocardial perfusion other than assessment of the end results of ischemia, such as wall motion abnormalities. Recent attempts at developing an effective contrast agent to measure myocardial perfusion have resulted in the development of microbubbles, unstable preparations of air trapped in fluid which serve as highly echogenic media. Clinical utility of contrast ultrasonography for measuring blood flow is critically dependent on the development of stable microbubbles that are small enough for unhindered capillary passage for intravenous injection.

The Phase I goal is to develop reproducible, stable, small, air-trapped spheres to serve as a perfusion contrast agent. The agent will optimally consist of 2.0-micron-diameter, air-trapped spheres, which will be tested for shelf-life and echogenic properties. When stable preparations are made, tests will be performed both *in vitro* and *in vivo* to demonstrate contrast efficacy.

The results of Phase I will serve as a basis during Phase II to perform full toxicity testing in rodents and dogs. After successful completion of toxicity testing, an Investigational New Drug (IND) application will be filed and clinical evaluation performed to obtain Food and Drug Administration approval. Successful development of a stable ultrasound contrast agent will have wide applicability, not only in monitoring cardiac perfusion but also in the assessment of tissue perfusion in other anatomic sites.

Title of Project: Bar-Coded Diet Analysis
Principal Investigator: Louise M. Caldarara, R.D.
Awardee Organization: Nutrition Scientific
1510 Oxley Street, Suite F
South Pasadena, CA 91030
Telephone Number: (818) 441-0021
Awardee Number: 1 R43 HL37875-01

This project will develop and test bar-coded pictorial booklets for through-the-mail use in surveys of food intake. Booklets will illustrate 400 food items and be used to obtain 24-hour diet recall data. The projected long-range use of booklets will be to identify groups of individuals with excessive total fat, cholesterol, and saturated fat intake in order to refer them for counseling. Bias and accuracy of booklets will be tested by 50 volunteers who record standard food models in duplicate. Bias and accuracy of booklets will be compared in duplicate with the standardized NHLBI-LRC 24-hour recall interview with 100 additional volunteers.

Title of Project: Fiber-Delivered Erbium:YAG Laser for Angioplasty
Principal Investigator: Martin G. Cohen, Ph.D.
Awardee Organization: Quantronix Corporation
P.O. Box 9014
49 Wireless Boulevard
Smithtown, NY 11788
Telephone Number: (516) 273-6900
Awardee Number: 1 R43 HL39349-01

A commercial model of an optically pumped, pulsed, Er:YAG solid-state laser will be modified and tested for beam performance and used in conjunction with a compatible low-loss, flexible, nontoxic, fluoride glass delivery fiber to study *in vitro* tissue interaction effects. The laser operates at an approximate wavelength of 2.94 μm on the $^4I_{11/2} \rightarrow {}^4I_{13/2}$ transition of trivalent erbium. Tissue interaction studies at this wavelength, which falls at the peak of the strong infrared-absorption band of water, have demonstrated efficient, ablative-type cutting with minimal thermal damage to surrounding areas. Optimization and refinement of the laser-tissue interaction, in particular as a function of pulse energy and temporal profile, are now required. Initial, direct-focused beam experiments are proposed, to be followed by testing of commercially available zirconium-fluoride glass fibers for laser damage and for efficacy in contact tissue machining *in vitro* in a wet field.

Favorable results will qualify the system for endoscopic applications in general laser surgery and, in particular, for catheter-guided angioplasty in peripheral and coronary vessels. The exacting requirements for removal of plaque in these latter applications demand precision cutting, and the Er:YAG laser would appear to be unique in its ability to provide this interaction via a flexible fiber.

Title of Project: Intraoperative, Regional Myocardial Blood Flow Monitor
Principal Investigator: Gerald Entine, Ph.D.
Awardee Organization: Radiation Monitoring Devices, Inc.
44 Hunt Street
Watertown, MA 02172
Telephone Number: (617) 926-1167
Awardee Number: 1 R43 HL38561-01

Coronary artery bypass is one of the most widely practiced procedures for the treatment of patients with coronary atherosclerosis, yet a simple and rapid method for assessing the effectiveness of the procedure while it is being performed is not currently available. It would be extremely useful if a direct measurement of regional myocardial blood flow (rMBF) could be made prior to the closing of the chest so that the need for any medical or surgical intervention could be identified during the procedure.

Radiation Monitoring Devices, Inc. proposes to develop a practical, cost-effective procedure to provide these data. The approach is based on nuclear medicine techniques using xenon-133 and a miniaturized solid-state detection system that would be suitable for use in the cardiac operating room.

By the end of Phase I, sufficient development should have been achieved with respect to protocol, detectors, instrumentation, and animal testing, that the feasibility of measuring rMBF intraoperatively should have been clearly demonstrated. This new monitoring capability will lead to important advancement in cardiac surgery as well as the creation of a potentially successful technical product.

Title of Project: Pediatric Intra-Aortic Balloon Pump
Principal Investigator: Jeffrey L. Orth
Awardee Organization: Rocky Mountain Research, Inc.
4249 South 3100 East
Salt Lake City, UT 84109
Telephone Number: (801) 466-8465
Awardee Number: 1 R43 HL35952-01A1

Intra-aortic balloon pumping (IABP) has become a standard treatment modality for cardiogenic shock in adults but has been used only sparingly in infants. This is due in part to the limitations of the currently available drive systems, which are designed to meet the physiologic needs of an adult.

A balloon pump, specifically tailored to the small volumes and higher rates often seen in pediatric cases, will be developed and tested on a mock circulation system. Comparisons to commercially available drive systems will be made *in vitro*, and the data will be validated by a series of *in vivo* experiments using dogs.

Appropriate IABP equipment may then be available for use in infants and children whenever low cardiac output syndrome is present. Additional clinical experience might then lead to expanded use in cases of myocarditis or sepsis.

Title of Project: Development of a Computerized Nasal Resistance System
Principal Investigator: Richard E. Frye
Awardee Organization: Sensonics, Inc.
15 South Haddon Avenue
Haddonfield, NJ 08033
Telephone Number: (609) 428-1161
Awardee Number: 1 R43 HL37911-01

Despite the fact that hundreds of thousands of Americans suffer from allergies, asthma, polyposis, nasal deformities, and other airway restricting maladies, there is presently no low-cost, commercially available, integrated computerized system for quantitatively assessing nasal airflow function. Quantitative normative data, based on male and female subjects with normal or abnormal nasal function, are not available for any measures of airflow derived from currently available commercial systems, and all such systems suffer from a number of technical and theoretical problems. The overall purpose of this project is to develop a low-cost, practical, and integrated computerized rhinometric system for which valid normative data are available.

In Phase I, Sensonics, Inc. will initiate the development of this system. In Phase II, the development of this system will be completed and population norms for individuals with normal and abnormal nasal function will be established.

Title of Project: Flow Cytometric Immune Monitoring in Cardiac Transplantation
Principal Investigator: James B. Peter, M.D., Ph.D.
Awardee Organization: Specialty Laboratories, Inc.
2122 Granville Avenue
Los Angeles, CA 90025
Telephone Number: (213) 478-1295
Awardee Number: 1 R43 HL38572-01

Successful organ transplantation requires sustained immunosuppression. Currently, immunosuppressive treatment for cardiac allograft recipients is determined empirically. Specialty Laboratories, Inc. has developed a sensitive and accurate technique to predict or confirm organ rejection and to discover if immunosuppressive treatment has modulated the immune response. Flow cytometric immune monitoring (FCIM) is a low-cost, sensitive, noninvasive assay that can detect opportunistic infections and predict transplant rejection.

Multiple-marker analysis will be performed on peripheral blood lymphocytes for the identification of activated circulating lymphocytes. FCIM can be utilized to monitor all transplant recipients for rejection and infection. This research will lead to a cost-effective, noninvasive, sensitive tool to predict all transplant rejections.

Title of Project: Nonsubtractive Magnetic Resonance Imaging of Blood Flow
Principal Investigator: D. N. Ghosh Roy, Ph.D.
Awardee Organization: Technical Research Associates, Inc.
410 Chipeta Way, Suite 222
Salt Lake City, UT 84108
Telephone Number: (801) 582-8080
Awardee Number: 1 R43 HL39346-01

Technical Research Associates, Inc. proposes to adapt digital transform technologies to improve upon the clinical effectiveness of angiographic imaging. This technology, when applied to magnetic resonance imaging (MRI), will permit the imaging of vasculature in isolation from the overlying bone and tissue structures without the necessity of applying cumbersome and inefficient subtraction techniques. The clinical use of MRI for vascular imaging has the added advantage of being noninvasive, as compared to x-ray imaging, which exposes the patient to hazardous, penetrating, ionizing radiation.

The objective of this project is to visualize the blood vessels while eliminating the unwanted superposition of extravascular bone and tissue structures, which is the central problem of angiography. Two-dimensional Fourier imaging is proposed for producing cross-sectional images using 180° rf-excitation and multislice Hadamard coding. Computer simulations and numerical implementations will be the main focus of Phase I work. Projection reconstruction imaging and experimental studies will be undertaken in Phase II.

Title of Project: Rapid Microhematocrit Determination Device
Principal Investigator: Stephen C. Peterson, Ph.D.
Awardee Organization: Technical Research Associates, Inc.
410 Chipeta Way, Suite 222
Salt Lake City, UT 84108
Telephone Number: (801) 582-8080
Awardee Number: 1 R43 HL37858-01

During Phase II development work on a continuous flow ultrasonic blood cell/plasma separator, Technical Research Associates, Inc. found that it was possible to compact the erythrocytes into bands in microhematocrit tubes. The process, using an ultrasonic standing wave, exerts forces sufficient to compact the erythrocytes to a volume fraction equivalent to that obtained in ordinary microhematocrit centrifuges. At the power levels required to achieve this "ultrasonic hematocrit," cavitation was not observed.

This new technique portends to development of a device that will, in a matter of seconds, provide hematocrit values from blood collected in microhematocrit tubes. This capability will allow emergency medical care personnel and others to quickly obtain useful cardiovascular system information. Because only small volumes of blood are required, this technique will likely find use in the treatment of neonates. Phase I will demonstrate the feasibility of the approach and provide the framework and data necessary to justify continued work. Phase II will develop a portable, hand-held hematocrit measuring device about the size of a digital multimeter, and containing no moving parts.

Title of Project: An Ultrasonic Platelet Harvester
Principal Investigator: Stephen C. Peterson, Ph.D.
Awardee Organization: Technical Research Associates, Inc.
410 Chipeta Way, Suite 222
Salt Lake City, UT 84108
Telephone Number: (801) 582-8080
Awardee Number: 1 R43 HL39361-01

Technical Research Associates, Inc. proposes the development of a novel platelet-harvesting system based on a previously developed ultrasound separation technology. This technology, developed under an NHLBI grant, allows the sequential separation of cells based on their size, even those cells that have identical densities.

First, residual erythrocytes and large leukocytes can be separated from platelet-containing plasma, thus reducing the concentration of these contaminants. Second, the platelets can be concentrated in the plasma by gently moving them to one end of a separation cell. This concentrative work is done without "packing" the cells into a pellet, thus reducing cell-cell interactions and presumably increasing platelet longevity. Platelet-rich plasma will then exit the device.

Title of Project: Implantable Blood-Volume Flowmeter for Small Vessels
Principal Investigator: Cornelis J. Drost, Ph.D.
Awardee Organization: Transonic Systems, Inc.
138 Langmuir Laboratory
Cornell Research Park
Ithaca, NY 14850-0238
Telephone Number: (607) 257-5300
Awardee Number: 1 R43 HL34920-01A1

This research aims to develop and validate a perivascular, blood-volume flowmeter for use in small animal models. Such an apparatus will facilitate new research because of its small-vessel (0.25 mm o.d.), low-flow (4 µl/minute) capabilities. Furthermore, it will allow the medical researcher to replace multianimal, acute studies with single-animal, chronic studies in those instances where anesthesia influences organ function. The flowmeter, a scaled-down version of apparatus currently manufactured by Transonic Systems, Inc., will utilize ultrasonic transit-time principles to measure volume flow directly, using nonconstrictive flow sensors to minimize alterations of the flow under study.

Phase I will address the feasibility of the plans. Prototype, miniaturized, flow sensors will be constructed and tested *in vitro* and *in vivo*, and manufacturing technologies will be evaluated. At two independent universities, chronic and acute research protocols using the prototype flow sensors will be initiated. During Phase II, Phase I design innovations will be incorporated into a prototype flowmeter. Acceptance of this flowmeter by the scientific community will be aided by continued collaboration with investigators on pilot research projects.

Title of Project: Expandable Laserprobe for Treatment of Coronary Disease
Principal Investigator: Hany Hussein, Ph.D.
Awardee Organization: Trimedyne, Inc.
1815 East Carnegie Avenue
Santa Ana, CA 92705
Telephone Number: (714) 261-9041
Awardee Number: 1 R43 HL37792-01A1

The specific aim of this project is to design, construct, and evaluate in animals an expandable laserprobe for treatment of occlusive coronary and peripheral artery disease.

The proposed device provides means for controlled application of heat and pressure to atherosclerotic tissue. The principle of operation involves the transmission of laser energy from source to patient and the rapid conversion of this energy into controlled thermal energy at the distal end of the probe. When brought into contact with occlusive tissue, this probe allows heat to be conducted rapidly to this tissue while maintaining a known pressure on the probe-tissue interface. This results in selective and controlled ablation of occlusive tissue with minimal thermal effect on surrounding tissue.

The basic design objective is to create an expandable laserprobe that can be introduced percutaneously and that alone can generate a sufficiently large lumen to permit adequate flow through coronary and peripheral arteries. The proposed laserprobe is expected to allow suitable patients to undergo a minimally invasive procedure for the relief of occlusive vessel disease in the legs and in the heart, resulting in significant reduction in the cost of health care for this ailment.

Title of Project: A Reliable, Simple, Electronic Pneumatic Pump Actuator
Principal Investigator: Robert L. Whalen
Awardee Organization: Whalen Biomedical, Inc.
5 Howland Street
Cambridge, MA 02138
Telephone Number: (617) 661-3693
Awardee Number: 1 R43 HL37879-01

The goal of the proposed program is the development of a portable, reliable, and simple electromagnetic pump driver for pneumatically actuated blood pump systems. This driver eliminates compressors, pressure regulators, solenoid valves, sliding seals, and any components subject to mechanical wear.

The basis of the design is an electromagnetically driven welded metal bellows. The total excursion and rate of movement of the bellows are electronically controlled using a closed-loop network which monitors bellows position and internal pressure. This microprocessor-based control system permits flexible operating modes, including fixed rate, autonomous variable rate, and passive synchronous and EKG-triggered synchronous counterpulsation at any desired stroke volume. It also allows for direct specification of the pressurization envelope to the blood pump, eliminating excessive systolic rates of pressurization or high diastolic negative pressures, either of which can produce hemolysis.

By virtue of its extreme mechanical simplicity, the driver is inherently reliable. Its target electromechanical efficiency of 20 percent will also result in a compact and portable pump driver that is low in cost compared to the bulky and mechanically complex systems currently available.

Phase II Grants

Title of Project: Emergency Ventilatory Support Devices Based on Hydrogen Peroxide
Principal Investigator: Kenneth Abel
Awardee Organization: The ABEL Company
SR 774 Box 267
Pembroke, VA 24136
Telephone Number: (703) 626-3036
Awardee Number: 2 R44 HL35148-02

The general aim of this effort is the development of one or more chemical oxygen delivery systems using hydrogen peroxide as the oxygen storage medium. Results of studies during Phase I demonstrated that a compact system using the controlled catalytic decomposition of hydrogen

peroxide can be developed which will retain the reliability of chemical systems for long, unattended storage while approaching the cost competitiveness and convenience of the more familiar compressed gas cylinders. The specific aim of this project is the development, testing, and demonstration of an oxygen generator designed specifically for applications in which long storage life, moderate to large generation capacity, simplicity of use, reasonable cost, and/or safety are of importance.

Title of Project: Oxygen Generator for Ambulatory COPD Patients
Principal Investigator: Kenneth Abel
Awardee Organization: The ABEL Company
State Route 774, Box 267
Pembroke, VA 24136
Telephone Number: (703) 626-3036
Awardee Number: 2 R44 HL36599-02

The specific goal of this research is the development of a portable oxygen source suitable for use in providing supplemental oxygen to individuals with chronic obstructive pulmonary disease (COPD) resulting from chronic bronchiolitis, pulmonary emphysema, asthma, or chronic bronchitis. The concept is based on the use of a common, low-cost, household chemical that generates oxygen when water and a suitable catalyst are added.

Title of Project: Developing and Marketing an Asthma Self-Management Program
Principal Investigator: John A. Winder, M.D.
Awardee Organization: Allergy & Asthma Consultants
5300 Harroun Road, Suite 101
Sylvania, OH 43560
Telephone Number: (419) 385-5755
Awardee Number: 2 R44 HL34277-02A1

The purpose of this project is threefold. During Part I, the existing educational materials of the classroom-style, asthma self-management program, Wheezers Anonymous (WA), will be modified and refined.

Part II will feature application of the WA self-management program to asthmatic adults. The experimental design involves a random assignment of subjects to either an intervention group or a waiting-list control group. Following acquisition of self-management skills, all subjects will be followed for at least 1 year to determine the effectiveness of the program over time. A major aim of this study will not only be to assess the retention of skills taught, but the actual performance of these skills over time. Concurrently, Part III will develop WA into a commercially applicable concept that is readily adaptable to a broad range of health care facilities.

Subject data will be analyzed using repeated-measures analysis of variance to assess possible differences between (1) groups and (2) treatment components. Each individual subject's data will also be analyzed separately from the beginning of his or her participation in the program.

Title of Project: Chronic Data Acquisition System and Playback to Computer
Principal Investigator: Edmond J. Dougherty
Awardee Organization: August Design and Development
300 East Lancaster Avenue, Suite 206
Wynnewood, PA 19096
Telephone Number: (215) 642-4000
Awardee Number: 2 R44 HL36065-02

The design, fabrication, and evaluation of a Biological Data Acquisition and Recording System for Cardiac Rhythm (BIDARS/CR) is proposed. This is a new, long-term ambulatory-patient monitoring system for subjects with known or possible rhythm disturbances. BIDARS/CR can provide patient surveillance for a minimum of approximately 18 days with a maximum exceeding 3 months. It has direct application for diagnostic purposes and for evaluation of therapy efficacy in the arrhythmic subject.

The system consists of a small, lightweight, and unobtrusive patient-worn monitor with a base station. The monitor contains a unique, micropowered, digital recorder that records ECG complexes immediately before, during, and after arrhythmic disturbances. BIDARS/CR also records the number of premature beats and the heart rate versus time. The base station is a standard PC with a BIDARS interface card and software, which permits the user to test and program the monitor, and analyze and store the collected data.

During the project, 20 monitors will be built. The system's ability to analyze, record, and play back cardiac rhythm abnormalities will be evaluated by using simulated rhythms, and by testing the system with patients undergoing electrophysiologic studies and patients wearing Holter and transtelephonic monitors.

Title of Project: Cardiovascular Health Education Software
Principal Investigator: Darwin Dennison, Ed.D.
Awardee Organization: DineSystems, Inc.
5 Bluebird Lane
West Amherst, NY 14228
Telephone Number: (716) 834-3463
Awardee Number: 2 R44 HL35892-02

This project will validate the DINE System, an activity and dietary recording and nutrient analysis procedure, for use in health education and nutrition research and demonstration projects. The completed protocol will consist of a standardized microcomputer-assisted procedure for use by sixth-grade students to accurately: (1) record daily food intake, (2) code food records, and (3) input and verify on-screen data. An in-service program will be designed to instruct teachers to conduct the five-lesson module, prompt the children to complete the records, teach accurate coding, assist the children with the input and verification of data, and store the data on classroom data disks. These data will determine if the natural environment of the classroom can be used to collect valid and reliable nutrient data.

A two-period cross-over design will be used to compare the developed microcomputer-based protocol with an established data collection mainframe-based protocol. Two hundred sixth-grade students from three middle schools will comprise the sample. The research question is: "Can teachers, in the natural environment of the classroom, assist children to collect data that are valid and reliable with data collected via a more labor-intensive interviewing procedure?" The present NIH research protocol suggests that nutrient data can be collected via interview and analyzed via mainframe computer procedures. The proposed data collection method, if valid, will be considerably less expensive than the standard protocol.

Title of Project: ELCA Assay of Clinically Important Clotting Factors
Principal Investigator: George J. Doellgast, Ph.D.
Awardee Organization: Elcatech, Inc.
4291 Lantern Drive
Winston-Salem, NC 27106
Telephone Number: (919) 924-4277
Awardee Number: 2 R44 HL35990-02

A novel methodology has been developed to assay clotting factors, using fibrinogen as a substrate. Two forms of fibrinogen are prepared, one having fibrinogen noncovalently associated with a solid phase (microtiter plates), and the other having fibrinogen covalently associated with an enzyme in solution phase. When the two forms are converted to fibrin, the enzyme label associates with the solid phase. This technique has been named enzyme-linked coagulation assay or ELCA.

Thrombin and any enzyme or cofactor that affects the generation of thrombin from plasma can be assayed using this methodology, at a sensitivity much higher than any other available technique, and at very low reagent cost. This project aims at converting this potential into a useful system for measurement of clotting factors and effectors. Reagent mixtures, which will consist of peroxidase-fibrinogen mixed with purified factors of substrate plasmas specific for a factor of interest, will be developed for all clotting factors of clinical interest. Samples will be diluted, and reagents will be added using a robotic system designed to be used in microtiter plate assays. Results will be read using a new, rapid microplate reader that permits kinetic analysis rather than endpoint readings.

The combination of high-assay sensitivity by using the ELCA methodology and convenience of sample handling and data manipulation by using automated systems will considerably improve the quality of analysis of clotting factors and effectors.

Title of Project: Measurement System for Passive Respiratory Mechanics
Principal Investigator: Alex Stenzler
Awardee Organization: Equilibrated Bio Systems, Inc.
900 Walt Whitman Road
Melville, NY 11747
Telephone Number: (516) 673-6630
Awardee Number: 2 R44 HL34900-02

The long-term objective of this project is to develop an automated, simple-to-use system for the measurement of respiratory mechanics in newborns and children with a passive expiratory maneuver.

Flow-volume measurements following relaxation of the respiratory muscles with the Hering-Breuer reflex allow for calculation of total compliance and resistance using the end inspiratory plateau pressure as the mean pleural pressure. Previously described application of this technique used manual controls for shutter closure and data analysis, limiting the method research only to applications.

Special design considerations in Phase II have provided for managing the low dead-space requirements while interfacing to a ventilator circuit. An automated system would place this technique within the reach of clinicians for the diagnosis and management of newborns and infants with altered lung function.

Title of Project: Detection of Theophylline in Serum
Principal Investigator: John Rebar, Jr., Ph.D.
Awardee Organization: Genesis Labs, Inc.
5182 West 76th Street
Minneapolis, MN 55435
Telephone Number: (612) 835-3421
Awardee Number: 2 R44 HL34294-02

Genesis Labs, Inc. has exclusive patent rights to a novel enzyme immunoassay dipstick. This method has been reduced to practice for serum theophylline and whole blood theophylline in the required therapeutic range of 2 to 40 µg/ml. An exciting aspect of this effort is the ability to provide the physician with a simplified assay system that does not require washing and separation steps. The result is available within 2 minutes, allowing the treating physician to make rapid adjustments in drug regimens while the patient is still in the doctor's consulting room.

In Phase II, Genesis Labs, Inc. intends to build on the progress made in Phase I in the fol-

lowing ways: (1) to investigate different formats of the assay; (2) to scale up reagent production; (3) to examine alternative signal-generating systems; (4) to modify current instrumentation, making it suitable for patient evaluation within a doctor's office; (5) to conduct pilot-scale manufacturing; and (6) to initiate preliminary clinical studies for FDA approval. Assays of this type will have considerable and favorable impact on health care cost-containment policies without lessening the quality of care currently provided by health service personnel.

Title of Project: Clinical Blood Viscometer
Principal Investigator: Reuben E. Kron, M.D.
Awardee Organization: KDL Technologies, Inc.
219 North Broad Street, Suite 200
Philadelphia, PA 19107
Telephone Number: (215) 893-7866
Awardee Number: 2 R44 HL35021-02A1

Increased blood viscosity is an important factor in the pathology of vascular diseases of atherosclerotic origin, such as peripheral vascular disease. However, blood viscosity measures are now rarely used because no suitable, inexpensive, and convenient clinical instrumentation exists for its measurement, and because up to now effective treatment for viscosity reduction was not available. Recently, pentoxifylline, the first drug specifically developed for viscosity reduction, has been introduced in the United States as a treatment for peripheral vascular disease. This is creating a large potential market for suitable viscometric instrumentation to be used for diagnosis and management of these patients.

The Phase I project has proven the value and utility of a new design concept for a fresh-whole-blood viscometer that is safe, accurate, inexpensive, portable, easy to use, and consists of disposable elements. The viscometer incorporates an analysis system that gives an instantaneous output of viscosity values that have direct clinical utility in monitoring treatment with viscosity-reducing drugs.

Phase II will be directed to completing the design and testing prototypes of this instrument, and to demonstrating its utility in the diagnosis and management of peripheral vascular disease.

Title of Project: Permanent Aortic Balloon Pump
Principal Investigator: Adrian Kantrowitz, M.D.
Awardee Organization: I. VAD TECHNOLOGY, Inc.
70 Gallogly Road
Pontiac, MI 48055
Telephone Number: (313) 493-6440
Awardee Number: 2 R44 HL39250-02

The objective of this Phase II project is to qualify the permanent aortic balloon pump for clinical trial in intractable left-ventricular failure (LVF). The system provides a distinctive balance of benefits and low risk, and it is expected to become an accepted therapy for chronic congestive LVF. The permanent aortic balloon system supports the left ventricle at therapeutically effective levels while maximizing patient safety. It is unique among left-ventricular assist systems in that its continuous pumping action is nonobligatory. The patient can be untethered for hours.

During Phase I, the redesigned blood pump was successfully tested in 5 calves, pumped intermittently without anticoagulant therapy over a 6-week period. In Phase II, the specific aims are to: (1) confirm and quantitate hemodynamic effects of the permanent aortic balloon in calves in which acute heart failure has been induced; (2) characterize the performance limits of the system; (3) demonstrate *in vitro* component reliability over a 2-year design life; (4) test and document the reliability and safety of the system in long-term (6-month) tests in each of 8 animals; and (5) develop an investigational plan, protocols, and a consent form to obtain approval by hospitals and the Food and Drug Administration for trial in human subjects.

Title of Project: Ultrahigh-Speed Storage for Minimally Invasive Imaging
Principal Investigator: Eric J. Siskind, Ph.D.
Awardee Organization: NYCB Real-Time Computing, Inc.
18 Meudon Drive
Lattingtown, NY 11560-1025
Telephone Number: (516) 759-0707
Awardee Number: 2 R44 HL36022-02

NYCB Real-Time Computing, Inc. proposes to develop a system for rapid storage and retrieval of very large quantities of digital image data such as might be found in the next generation of digital-subtracted angiography systems, designed for minimally invasive imaging of the coronary arteries or other deep arteries. The image mass-storage system is to be constructed by interfacing an array of latest generation, parallel-transfer computer disks to a very high-bandwidth data acquisition and computer interconnection bus (the Fastbus, IEEE Standard 960, developed by the National Bureau of Standards and the Department of Energy) to meet the substantial computing needs of the next generation of experiments in elementary particle physics. The resultant data acquisition and storage system features data transport approximately 16 times faster and data storage at least 4 times faster than the current generation of 30 frames/second, 512 × 512 pixels/frame, digital radiography systems just becoming commercially available.

It is expected that Fastbus technology could be rapidly integrated into commercial radiography systems once the increases in framing rate, spatial resolution, and/or video signal-to-noise ratios warrant such enhancements in performance requirements of image storage systems.

Title of Project: Ventricular Function Monitor for Active Patients
Principal Investigator: Michael Squillante, Ph.D.
Awardee Organization: Radiation Monitoring Devices, Inc.
44 Hunt Street
Watertown, MA 02172
Telephone Number: (617) 926-1167
Awardee Number: 2 R44 HL32370-02A1

An improved technique to measure the ventricular-ejection fraction of cardiac patients over a continuous period of many hours of normal daily activity or during prescribed exercise is needed. Radiation Monitoring Devices, Inc. proposes to develop a comfortable, vest-like instrument that measures the left-ventricular ejection fraction. This instrument will be able to electronically track the radioactive emission of technetium-99m within the left-ventricular blood pool, regardless of the repositioning of the heart due to posture changes or accelerative motions. The basic concept has been explored in collaboration with Massachusetts General Hospital and the results appear very promising. In Phase I, the necessary advances were made to now proceed with the design of a compact, lightweight, and portable Anger detector using large-area, silicon avalanche photodiodes.

In Phase II, a ventricular-function monitor using a very lightweight Anger detector to greatly increase the ambulatory capability will be designed and built. Clinical tests of this vest will be made by Massachusetts General Hospital.

Title of Project: Audiovisuals for Blood Pressure Training and Testing
Principal Investigator: Carlene M. Grim
Awardee Organization: Shared Care Productions
25 Coveview Drive
Rancho Palos Verdes, CA 90274
Telephone Number: (213) 544-3207
Awardee Number: 2 R44 HL35889-02

The long-term goal of this proposal is to develop, produce, and distribute high-quality, state-of-the-art, scientifically sound audio-visual materials and computer software for teaching correct blood pressure measurement. The programs will be used to teach patients, professionals, and researchers according to established guidelines, and to test persons who measure blood pressure for performance according to recommended standards.

Phase I demonstrated the need and feasibility of producing these programs in both computer-assisted and laser disk formats by adapting existing state-of-the-art video-taped programs. These audiovisuals will be updated to meet changing guidelines, and additional blood pressure readings will be recorded using the techniques perfected during Phase I. After prototypes are developed and tested, the final versions will be prepared for distribution. Testing will be done in selected schools of medicine and allied health.

Title of Project: Development of a Highly Compliant Vascular Graft
Principal Investigator: Philip Litwak, D.V.M., Ph.D.
Awardee Organization: Thoratec Laboratories Corporation
2023 Eighth Street
Berkeley, CA 94710
Telephone Number: (415) 841-1213
Awardee Number: 2 R44 HL34933-02

A new, highly compliant vascular graft has been fabricated from a unique polyurethane material. Prototype grafts have demonstrated excellent blood compatibility and no perigraft reaction. The maximum thickness of endothelial and subintimal tissues bridging the anastomoses have been 15 to 20 microns, and in some cases, only a continuous monolayer of endothelial cells has been found.

Bulk and surface properties required of this material have been decoupled and developed independently in two separate materials. The final polymer consists of a blend of surface active copolymers and bulk material to produce a formulation optimized for this specific use.

Four-mm diameter vascular grafts will be produced using Thoratec Laboratories Corporation's patented process for fabrication of multilayered tubing. These grafts will be tested both *in vivo* and *in vitro*. *In vitro* testing will include compliance, burst strength, kink radius, elongation, and suture pullout strength. Grafts will be tested before and after sterilization. Lifetesting will also be accomplished.

In vivo evaluation will be accomplished by implanting 8-cm lengths in the carotid arteries of mature goats and as aorto-coronary bypasses in calves. ^{99m}Technetium scanning will be used to determine patency. Explanted grafts will be resubjected to the *in vitro* test protocol, as well as SEM and standard microscopic examination.

Title of Project: Expression of Human Protein C in Mammalian Cells
Principal Investigator: Mark J. Murray, Ph.D.
Awardee Organization: ZymoGenetics, Inc.
2121 North 35th Street
Seattle, WA 98103
Telephone Number: (206) 632-4036
Awardee Number: 2 R44 HL36496-02

Human protein C is a vitamin K-dependent plasma protein involved in the control of blood coagulation and fibrinolysis. An expression system for the production of recombinant human protein C has been established. This system is based on mammalian cells in culture, stably transfected with a DNA construction expressing human protein C. This expression system se-

cretes into the culture media approximately 400 µg/L of protein C that is gamma carboxylated, completely processed to its two-chain form, and capable of full biological activity.

Methodologies, including random integration screening, gene amplification, and dicistronic mRNA constructions will be used in this research to increase the expression level of protein C. Some innovative modifications will be made to the expression construction to produce protein C molecules that will be more efficiently processed, gamma carboxylated, or activated during secretion. The goal is to establish a development-scale expression system to produce human protein C for various therapeutic applications.

Phase I Contract

Title of Project: CAI Modules on CVD Nutrition
Principal Investigator: Teresita B. Hernandez, Ph.D.
Awardee Organization: JWK International Corporation
7617 Little River Turnpike, Suite 800
Annandale, VA 22003
Telephone Number: (703) 750-0500
Awardee Number: 1 N43 HC75077-00

The overall objective of this project is to develop a series of interactive self-instructional modules for the teaching of cardiovascular nutrition to senior medical students. When fully developed, the modules can also be used by residents and physicians in general medical practice.

The specific objective in Phase I is to develop a computerized catalog of existing educational materials on cardiovascular nutrition. These include printed materials, such as professional manuals, consumer education materials, textbooks, and journal articles, as well as other media materials such as videotapes, slide presentations, and films. The computerized file will be indexed by content, instructional medium, target audience, contact hours, developer, year of development, availability, and cost.

In addition to the computerized catalog of educational materials, a plan for developing and testing the computer-assisted instruction (CAI) modules in Phase II will be developed in Phase I. The technical objective of Phase I will include a demonstrable interactive program for a simple case study. This will illustrate not only the feasibility of the plan, but also provide an estimate of the time and resources needed to develop realistic work scope and cost estimates for Phase II.

Phase II Contracts

Title of Project: Assay Methods to Detect Cytomegalovirus
Principal Investigator: John Todd, Ph.D.
Awardee Organization: Enzon, Inc.
Middlesex Business Center
300-C Corporate Court
South Plainfield, NJ 07080
Telephone Number: (201) 668-1800
Awardee Number: 1 N44 HB77028-00

Cytomegalovirus (CMV) infections are common, but not usually life threatening in healthy adults. However, neonates and immunocompromised individuals who are infected with this herpes virus develop serious and sometimes fatal respiratory and neural disorders. Transmission of CMV by blood transfusion is common. Clinically relevant tests for detecting CMV directly in blood and other body fluids are not available.

In Phase I, Enzon, Inc. established the feasibility of detecting CMV DNA in a model cell culture system and in lung biopsy specimens from CMV sero-positive patients using an *in situ* DNA hybridization format. Optimal sample fixation,

hybridization, and detection conditions were established with two CMV-specific DNA probes.

In Phase II, these conditions will be used to develop novel, rapid, reliable, and user-friendly nonradioactive DNA hybridization assays for the direct detection of CMV in blood, enriched lymphocyte preparations, urine, bronchial washes, and lung biopsy specimens. *In situ* and/or dot-blot assay formats will be devised, then used to analyze clinical specimens from CMV sero-positive and sero-negative individuals. The results of these tests will be compared to those obtained using cell culture and immunological assays for CMV to determine the efficacy of DNA-based assays for diagnosing past and present CMV infections.

Title of Project: Procurement of Primary Reference Materials
Principal Investigator: Kathleen A. White
Awardee Organization: MERCOR, Inc.
2448 Sixth Street
Berkeley, CA 94710
Telephone Number: (415) 849-0452
Awardee Number: 1 N44 HV76101-00

Polyurethanes are used in a variety of biomedical devices, including artificial hearts, vascular grafts, catheters, and intra-aortic balloons. This proposal presents methods for the synthesis, characterization, and fabrication of three polyurethaneurea Primary Reference Materials (PRM).

The proposed program involves the synthesis of three additive-free polyurethaneureas followed by thorough characterization of the bulk and surface properties of cast films. By varying the type of soft segment in the polyurethaneurea, the surface tensions will be 23 dynes/cm for polydimethylsiloxane (PSX), 32 dynes/cm for polytetramethylene oxide (PTMO), and 44 dynes/cm for polyethylene oxide (PEO). The polymers will be converted into tube and sheet configurations under controlled and documented conditions. Bulk and surface physicochemical characterization will be applied to assess changes induced by the conversion process, packaging, and sterilization.

During Phase I of this contract, a limited amount of the PTMO-based polyurethaneurea PRM was prepared. Phase II will involve the manufacture, characterization, and sterilization of PTMO-based PRM, PEO-based PRM, and PSX-based PRM. A documentation package will be provided with the PRM, which will contain the characterization results, and handling and storage instructions. Selected characterization will be performed at regular intervals to determine if the bulk or surface properties of the PRM are affected by storage.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Phase I Grants

Title of Project: Stimulus Pairs in 3D Auditory Brainstem Response
Principal Investigator: Barbara Silverberg
Awardee Organization: ABRATECH Corporation
100 Bush Street, 26th Floor
San Francisco, CA 94104
Telephone Number: (415) 394-7346
Awardee Number: 1 R43 NS24476-01

The goal of this research is to determine the feasibility of combining three-channel recording of the auditory brainstem response (ABR) with a stimulus-pairs technique so as to measure the decrement in response that occurs in the relative refractory period (RRP). This method will permit detection of any abnormalities that affect the RRP, as the parameters can be adjusted so that there is decrement in the response to the second stimulus, in normals. The three-channel Lissajous trajectory of the ABR will be analyzed with respect to both linear and planar segments. The use of stimulus pairs provides information about the responses to both the first and the second stimulus (in the RRP). This methodology is likely to be more sensitive to pathological changes in the auditory nervous system than is the ABR, which has had extensive use in audiology and neurology as an objective measure of brainstem normality or abnormality.

Title of Project: Nontoxic Resorbable Collagen Prostheses to Aid Peripheral Nervous System Repair
Principal Investigator: Shu-Tung Li, Ph.D.
Awardee Organization: American Biomaterials Corporation
105 Morgan Drive
Plainsboro, NJ 08536
Telephone Number: (609) 683-0900
Awardee Number: 1 R43 NS25344-01

The central purpose of this research is to test the efficacy of a collagen-based tubular prosthesis to promote axonal regeneration in the peripheral nervous system *in vivo*. The prosthesis is nontoxic and biodegradable and is fabricated from natural connective-tissue components. During Phase I, American Biomaterials Corporation will continue studies in rodents, while Phase II will concentrate on nonhuman primates and potential human clinical trials.

Using both anatomic and physiologic techniques, American Biomaterials Corporation will quantify and directly compare current standard nerve-repair procedures with the new proposed tubular prosthesis. The first specific aim will focus on the production and quality-control testing of collagen-based nerve guides. Other specific aims will involve biological testing of the nerve guides and a critical comparison of peripheral nerve repair using standard clinical nerve microsuture and grafting procedures versus entubulation repair with the collagen-based prosthesis. Such quantitative comparisons have direct clinical relevance to human peripheral nerve repair.

Title of Project: Combined Tactile Aid and Classroom FM Auditory Trainer
Principal Investigator: David Franklin
Awardee Organization: Audiological Engineering
9 Preston Road
Somerville, MA 02143
Telephone Number: (617) 623-5562
Awardee Number: 1 R43 NS25345-01

The long-range goal of this project is to enable the implementation of a tactile FM trainer consisting of an FM receiver, a five-channel tactile aid, and a high-gain bilateral hearing aid as an integral unit for use by severely and profoundly deaf children. The immediate goals are to assess the technological possibilities for designing such a unit in an acceptable size, to verify the adequacy of the five-channel tactile-aid processing scheme for this application, and to gain assurance that the three circuits will operate from a single battery supply without adverse interactions.

The need for a combined tactile aid/auditory trainer has become evident from the fact that more than one-half of the tactile aids sold to schools have been accompanied by requests for information as to how they can be made compatible with FM systems. While this can be done, it requires that the child wear two body-type devices (a tactile aid and a separate FM trainer), which is inconvenient for both the child and the teacher. Furthermore, the available tactile aids are not ideal for this application. As tactile aids become more commonly used and as training techniques advance, the need for this integrated system will clearly increase.

Title of Project: Neuroanatomy Workstation and Knowledge Engineering
Principal Investigator: Wade K. Smith, M.D.
Awardee Organization: Biographics, Inc.
7040 Oak Bluff
Dallas, TX 75240
Telephone Number: (214) 387-2775
Awardee Number: 1 R43 NS25321-01

This project will explore the development of an advanced, low-cost computer system, based on a virtual-memory Intel 80386 processor, for image analysis, graphical data storage, and three-dimensional reconstruction that will be used as a neuroanatomical workstation. The station will include provisions for data input from a digitizing tablet, computer microscopy using a light microscope with stepper motor stage, and autoradiography analysis with a video camera and light box. A modeling and reconstruction package will feature solid-body graphical imaging, and a standardized database format will promote data archiving and exchange among a community of users.

The aims of this project are: (1) to put existing software and test capabilities on a 80386-based system, (2) to design future software development for a "neuroanatomist's notebook," and (3) to examine the feasibility of applying advanced system features and knowledge representation techniques for later development in Phase II.

Title of Project: Noise Reduction for Magnetoencephalography
Principal Investigator: Duane B. Crum, Ph.D.
Awardee Organization: Biomagnetic Technologies, Inc.
4174 Sorrento Valley Boulevard
San Diego, CA 92121
Telephone Number: (619) 453-6300
Awardee Number: 1 R43 NS24484-01

Magnetoencephalography (MEG) is the noninvasive magnetic measurement of electrical current within the brain which is believed to give significant new information about brain function that complements other modalities such as EEG and PET. Using MEG, sources of normal and pathological brain activity have been localized to a few millimeters in three dimensions. The MEG bandwidth extends down to dc to allow evaluation of injury currents and very low-frequency changes in neuronal activity.

Environmental noise is frequently the limiting factor for MEG measurements. The goal of this project is to improve the MEG signal-to-noise ratio by a combination of shielding, instrument design, and signal processing. Successful outcome of this work will be especially beneficial to measurements of spontaneous MEG where signal averaging is not feasible and to detection of signals from subcortical sources.

This project has immediate significance in the clinical evaluation of epilepsy patients being considered for surgical treatment. Other potential areas of benefit include evaluation of neuromuscular disorders and observation of dc currents associated with spinal cord injuries.

Title of Project: A Digital Signal Processing Evoked-Potential Machine
Principal Investigator: Joseph A. Sgro, Ph.D.
Awardee Organization: Corteks, Inc.
84 Old Farm Road North
Chappaqua, NY 10514
Telephone Number: (212) 795-1484
Awardee Number: 1 R43 NS24494-01

Currently available evoked-potential machines generally rely on ensemble averaging to separate the evoked-potential waveforms from accompanying noise. This technology imposes limits on the utility of these systems in "high-noise" environments and when rapid resolution of potentially changeable evoked potentials is clinically essential, such as in the operating room or the intensive care unit.

Corteks, Inc. proposes the development of an evoked-potential machine which will utilize a combination of digital signal processing techniques to resolve evoked-potential waveforms more rapidly and with substantially less noise contamination than currently available commercial systems.

During Phase I, Corteks, Inc. will implement and critically evaluate a real-time prototype. In Phase II, the array processor used in the Phase I prototype will be replaced with a superior and lower cost device and automatic optimization algorithms to simplify use.

Title of Project: A Magnetic Neural Stimulator for Neurophysiology
Principal Investigator: Joseph A. Sgro, Ph.D.
Awardee Organization: Corteks, Inc.
84 Old Farm Road North
Chappaqua, NY 10514
Telephone Number: (212) 795-1484
Awardee Number: 1 R43 NS24924-01

Corteks, Inc. proposes to develop a compact, moderately priced, magnetic neural stimulator for neurophysiology. The device will overcome several limitations inherent to electrical stimulation. By permitting pain-free, noninvasive stimulation of deep-lying peripheral nerves and spinal roots, as well as facilitating certain somatosensory evoked potential studies, this device will substantially expand the scope of clinical neurophysiological testing. In addition, the device will be capable of transcranial cortical stimulation, allowing the evaluation of descending motor pathways.

In Phase I, a prototype neural stimulator will be constructed, incorporating several improvements over previously published designs. It will be used to experimentally determine the optimal ranges of certain magnetic pulse parameters for stimulation of neural tissue.

In Phase II, an optimized stimulator designed using Phase I results will be constructed and fully tested. Considerations regarding transcranial cortical stimulation will be addressed.

Title of Project: A Self-Optimizing Evoked-Potential Amplifier
Principal Investigator: Joseph A. Sgro, M.D., Ph.D.
Awardee Organization: Corteks, Inc.
84 Old Farm Road North
Chappaqua, NY 10514
Telephone Number: (212) 795-1484
Awardee Number: 1 R43 NS24490-01

Corteks, Inc. proposes to develop a microprocessor-controlled self-optimizing amplifier specifically designed to record evoked potentials under adverse conditions. The device will have very high common-mode-noise rejection, superior anti-aliasing, and reduced susceptibility to stimulus artifact compared to current commercial devices. It is anticipated that these features will make this amplifier significantly better suited for recording evoked potentials in electrically noisy environments, and for performing evoked-potential studies which are currently difficult or impossible because of stimulus artifact.

These performance characteristics will be achieved by incorporating several digitally controlled analog components in critical places in the amplifier circuit, and using an onboard dedicated microprocessor to optimize amplifier function.

In Phase I, an initial prototype will be designed and built, and the effectiveness of the proposed techniques will be critically evaluated. In the Phase II prototype, the simple digital passband filter used in Phase I will be replaced with a substantially more powerful digital signal processor to enhance the amplifier input switch to support automatic rapid montage switching. The role of the microprocessor will expand to provide stimulator control.

Title of Project: Computer-Based Interactive Home Trainer for Deaf Speech
Principal Investigator: David C. Coulter
Awardee Organization: Coulter Associates
9613 Pembroke Place
Vienna, VA 22180
Telephone Number: (703) 759-5992
Awardee Number: 1 R43 NS24510-01

In Phase I, Coulter Associates will demonstrate the feasibility of a personal computer-based system for speech practice at home by severely/profoundly deaf children. This system is to be used in conjunction with a school/clinic system, and both systems are currently under development. Severely/profoundly deaf children cannot achieve intelligible speech without long-term intensive speech therapy. The home speech-training system is designed to give practice and help achieve carryover from therapy, an effect difficult to achieve with conventional methods.

Work will involve: (1) prototype production of a speech data acquisition system on printed circuit boards; (2) development of training games involving spectral (vowel), intensity, duration, and voice pitch parameters; (3) analysis of vocalizations; and (4) evaluation of interactions between the main computer and co-processors. Phase II will expand the number of training games for the home and school systems, carry out an evaluation program of both systems in terms of their effects on speech communication of deaf children, and update the hardware configuration.

Title of Project: Cordless, Full-Duplex, Hands-Free-Operation Speakerphone
Principal Investigator: Eric R. Hansen
Awardee Organization: Diversified Technology, Inc.
14167 Meadow Drive
Grass Valley, CA 95945
Telephone Number: (916) 477-1234
Awardee Number: 1 R43 NS25346-01

The severely disabled and motion-impaired often cannot operate currently available telephones. The expeditious development of usable, reliable, and accessible telephone equipment would prove cost effective by delaying or preventing institutionalization of the severely disabled for chronic health problems (e.g., residual bladder infections, respiratory infections, dysreflexia, and decubiti). Such institutionalization often occurs directly as a result of being unable to secure appropriate medical assistance by telephone.

Drawing upon knowledge of the quadriplegic's needs and basing research on current cordless-telephone technology, Diversified Technology, Inc. proposes to develop and integrate circuitry that will provide hands-free activation and operation, automatic dialing, and simultaneous reception and transmission. Designing a device small enough to allow portability will enhance and encourage independence and decrease the requirements and related costs of in-home care. Providing jacks for alternative switches and headsets will permit molding the device to the user's capabilities.

Though intended for the disabled, the possible applications in the commercial and residential markets for such an innovative telephone are numerous, and would include conference rooms, record-retrieval centers, beauty salons, medical clinics, telemarketing, and others.

Title of Project: Telephone Communication for the Deaf
Principal Investigator: William F. Duffy
Awardee Organization: Duffy Engineering
7 Nashawena Road
Mashpee, MA 02649
Telephone Number: (317) 477-3834
Awardee Number: 1 R43 NS23665-01A1

This proposal addresses the problem of telephone communication by the deaf and deaf-blind. The current state of the art allows these persons to communicate on the telephone with others when both are using specialized equipment. The proposed concept would require specialized equipment by the hearing-impaired person only.

The process is based on a commercial microcomputer converting tone or pulse signals into ASCII combinations. This ASCII code could then be converted to screen output or interfaced with a braille-output device (for the deaf-blind). A speech-output device could also be incorporated for speech-impaired persons. This ASCII conversion process would be inexpensive to produce once developed.

As the user would frequently be interacting with nondeaf persons, Duffy Engineering's system would be geared toward ease of use by the person without the specialized equipment.

Title of Project: Microelectrode Modification for Voltammetric Analysis
Principal Investigator: Joseph S. Foos, Ph.D.
Awardee Organization: EIC Laboratories, Inc.
111 Downey Street
Norwood, MA 02061
Telephone Number: (617) 769-9450
Awardee Number: 1 R43 NS25341-01

Microelectrodes and microelectrode arrays have been fabricated for use in living tissue for voltammetric analysis of biological fluids. The arrays are made on silicon substrates using the vacuum techniques employed in the electronics industry. These techniques are likely to be less useful when modifying the individual electrodes in an array due to the multiple operations required for each electrode.

In contrast, electrochemical modification would allow the individual address of each microelectrode and allow surface modification under mild conditions. EIC Laboratories, Inc. proposes to investigate a specific approach to the electrochemical modification of microelectrodes, with the goal of enhancing the voltammetric response of the electrodes toward specific neurotransmitters and other biologically important substances. This would allow analysis for neurotransmitters and other substances using multiple sensors in a microarray.

Title of Project: "Scrubless" Amplified Electrodes for Bioelectric Pickup
Principal Investigator: Mead C. Killion, Ph.D.
Awardee Organization: Etymotic Research, Inc.
61 Martin Lane
Elk Grove Village, IL 60007
Telephone Number: (312) 228-0006
Awardee Number: 1 R43 NS24911-01

The goal of this research is to determine the practicality of adding subminiature amplifiers to the electrodes used for Auditory Brainstem Response (ABR) recording in order to reduce or eliminate the need for scrubbing (often lacerating) the skin prior to electrode placement. If successful, the same amplifier system should also (1) permit more accurate "electrocochleography" recordings in front of the unpunctured eardrum where scrubbing the skin is impractical and the electrode size is too small to allow a low-resistance contact; (2) permit use in EKG and other long-term monitoring applications where present salt-jell systems sometimes cause skin irritation; and (3) permit more convenient myoelectric pickups for "bionic limb" developments.

A laboratory prototype has been successfully tested. A more sophisticated version suitable for universal plug-in replacement of present electrode systems is to be explored.

Title of Project: Neural Data Acquisition System for Multielectrode Arrays
Principal Investigator: Kenneth L. Drake
Awardee Organization: Integrated Microsystems, Inc.
2488 Autietam Drive
Ann Arbor, MI 48105
Telephone Number: (313) 996-5588
Awardee Number: 1 R43 NS24900-01

Multielectrode recording arrays that extract simultaneous neuroelectric activity have created a need for a computer-based data acquisition system. The arrays incorporate on-chip circuitry for buffering and multiplexing neural signals from several recording sites. The proposed system gives neurophysiologists the capability to investigate neural communicative processes, form neural process network models, and facilitate neural prostheses development.

The Phase I proposal implements an acquisition system and software based on an innovative application of a digital signal processor board as a preprocessor to a host computer. The system design is developed around the unique recording properties of multielectrode arrays to record single-unit action potentials simultaneously on several recording sites. The system's capabilities and limitations will also be assessed to determine the feasibility to perform real-time signal processing and analysis of multichannel neural data for an advanced Phase II system.

Successful implementation provides a commercial system that fills a gap in neurophysiology instrumentation. In addition, it provides a tool to collect and conduct more sophisticated analysis of multielectrode data.

Title of Project: Controlled Iontophoretic Delivery of Narcotics
Principal Investigator: Tomasz J. Petelenz
Awardee Organization: JMW Acquisition Company, Inc.
1290 West 2320 South, Suite A
Salt Lake City, UT 84119
Telephone Number: (801) 975-1191
Awardee Number: 1 R43 NS24315-01A1

The aim of this proposal is to investigate and develop long-term iontophoretic procedures for delivery of narcotic agents. Iontophoresis has been known for a long time, but its application is limited to short-term procedures (15 to 30 minutes). The major impediment to long-term use is the formation of electrolytic products at the electrode, lowering the efficiency of drug transport and causing burns. These problems have been addressed and long-term delivery has been studied both theoretically and experimentally with morphine as a model drug. As a result, treatment times have been extended up to 2 hours with significant morphine levels in blood and no complications.

The proposed study involves (1) laboratory *in vitro* determinations of iontophoretic electrode efficiency and delivery rates over long (12 to 24 hours) application times using an automated, computer-controlled sampling system; (2) animal experiments using nude rats with isolated skin flaps in order to determine long-term delivery rates with ^{14}C morphine HCl; and (3) a controlled, double-blind clinical study involving patients afflicted by severe postoperative pain. The result of these studies will be a new iontophoretic drug delivery system for narcotic analgesics, primarily morphine.

In Phase II, new electrode formulations and an iontophoretic control device will be designed, fabricated, and used in large-scale, long-term clinical trials.

Title of Project: An Instrument for Automated Auditory Screening of the Newborn
Principal Investigator: Keith H. Johnson
Awardee Organization: Metraco, Inc.
1100 Hercules, Suite 210
Houston, TX 77058
Telephone Number: (713) 488-5901
Awardee Number: 1 R43 NS24493-01

Metraco, Inc. proposes to develop a prototype evoked-potential instrument that will allow automated screening for hearing problems in the newborn infant. The instrument will provide new, unique features and technology unavailable in existing instruments. The major goals are: (1)

to improve the effective signal-to-noise ratio and error reduction ability by computation of the median rather than the mean evoked potential, allowing fewer stimuli to be used, thereby reducing the time of the test procedure; (2) to develop an automatic analysis system that will compare the values determined by the evoked-potential system against normative data to provide reliable screening for hearing deficits in the newborn, using predetermined pass/fail criteria; (3) to incorporate off-the-shelf microprocessors to reduce the cost to the end users; (4) to make the system simple to use, thereby permitting reliable operation by medical personnel without specialized training; and (5) to provide a written record of the test for analysis by the physician and as a follow-up for later treatment if required.

Phase I will be conceptual in nature and the instrument will be an engineering bench prototype only.

Title of Project: Tinnitus Suppression by Electrical Stimulation
Principal Investigator: David R. Wilkinson, Ph.D.
Awardee Organization: Neural Prosthetics Research, Inc.
2855 Folsom Street, #550
San Francisco, CA 94103
Telephone Number: (415) 476-5315
Awardee Number: 1 R43 NS24500-01

Chronic, intractable tinnitus disables more than a million otherwise healthy individuals in the United States. Neural Prosthetics Research, Inc. proposes to complete development of implantable electrical devices designed to suppress chronic high-tone tinnitus, while conserving residual hearing across the speech frequency range. Development of this device is based upon observations with cochlear implant patients studied at the University of California at San Francisco and at Duke University, as well as upon animal studies of auditory nerve suppression. The former studies have revealed that an appropriately stimulated cochlear prosthesis profoundly suppresses tinnitus. Both series of studies indicate that tinnitus can probably be effectively suppressed with minimal interference to hearing in more removed cochlear regions.

In these proposed device-development studies: (1) extracochlear stimulation sites effective for suppressing tinnitus will be defined; (2) optimum electrode configurations, stimulus forms, and stimulus sequencing will be defined for producing profound tinnitus suppression with minimal-level and minimum-period stimulation; and (3) models of suppression instruments suitable for application in an Investigational Device Exemption (IDE) clinical trial will be built.

These studies should lead to final specification of the design of a practical tinnitus instrument, effective for a large percentage of patients suffering from severe, intractable chronic tinnitus.

Title of Project: Automated Variable-Context Equilibrium Training
Principal Investigator: Lewis M. Nashner, M.D.
Awardee Organization: NeuroCom International, Inc.
9570 Southeast Lawnfield Road
Clackamas, OR 97015
Telephone Number: (503) 653-2144
Awardee Number: 1 R43 NS24509-01

The long-term goal of NeuroCom International, Inc. is to develop and market computer-automated systems for retraining posture and equilibrium functions in patients with a variety of disorders, including peripheral vestibular deficits, head injury, stroke, and age-related degenerative disorders. The proposed retraining system will be menu driven and operable by the patient under the supervision of a therapist. The protocols will help the patient learn to compensate for abnormal sensory interaction or movement coordination affecting posture. The quantitative measures provided will assist both therapist and patient in monitoring progress.

The Phase I grant period will produce a detailed product description for a commercially feasible, automated retraining system. Specific goals include: (1) defining protocols to improve functional balance skills by retraining specific components of abnormal sensory and motor function; (2) defining the means to provide patients with necessary feedback information during retraining; (3) defining algorithms by which the difficulty and scope of protocols can be automatically adjusted as the patient's performance improves; (4) defining absolute measures of performance by which to score the patient in relation to himself and age-matched normals; and (5) identifying the mechanical, electronic, and computer hardware necessary to implement the automated retraining protocols.

Title of Project: Multisite Optical Recording of Membrane Potential
Principal Investigator: Harry Fein
Awardee Organization: World Precision Instruments, Inc.
375 Quinnipiac Avenue
New Haven, CT 06513
Telephone Number: (203) 469-8281
Awardee Number: 1 R43 NS25199-01

The long-term objectives of this project are to improve optical methods for monitoring membrane potential. Present evidence suggests that these methods might be used in two clinical settings: first, to study the generation of arrhythmias and other abnormalities of action potential propagation in the heart; and second, to localize regions of epileptogenic foci in patients with epilepsy who require surgery.

The specific aims are to improve optical-measuring technology in three areas. First, to improve the dyes that transduce the changes in membrane potential into optical signals, it is proposed to synthesize new dyes of novel structural types. Second, to make the photodiode array and the associated amplifiers more flexible, reliable, and economical, it is proposed to start with an array with more elements to improve the spatial resolution. And third, to make the computer recording and analysis more powerful and economical, hardware and software for a 32-bit computer will be developed.

Optical monitoring of membrane potential is a new method that allows simultaneous monitoring from many sites. The proposed dyes, the modifications to the amplifier system, and the incorporation of a 32-bit computer into the laboratory would be technically innovative. If successful, these novel solutions would be part of apparatus that World Precision Instruments, Inc. would market to biologists and clinical scientists.

Phase II Grants

Title of Project: Automated Electrophysiological Hearing Screening Device
Principal Investigator: Edward Miskiel
Awardee Organization: Artificial Hearing Systems Corporation
1125 Northeast 125th Street, Suite 206
North Miami, FL 33161
Telephone Number: (305) 895-6500
Awardee Number: 2 R44 NS23666-02

Over the past decade, the use of auditory brainstem response (ABR) audiometry for diagnostic purposes has increased, and ABR audiometry has been widely accepted for both hearing testing and screening of newborn and older infants. Although the diagnostic value of the hearing evaluation technique has been realized, ABR testing and screening have not been widely implemented on a clinical basis, mainly because of the time and expense of current testing procedures. Testing with current ABR devices requires extensive professional involvement, which makes this procedure costly.

In Phase I, methods to automate ABR testing were investigated. In the proposed Phase II project, processing strategies for improving the performance of a prototype ABR device will be refined and a cost-effective, dedicated, portable ABR screening-device prototype will be built and tested.

This microcomputer-based ABR device will reduce both testing time and clinician involvement. To achieve this end, (1) response acquisition will be further improved; (2) the response detection algorithm developed in Phase I will be implemented on-line; (3) processing algorithms will be further improved as a result of extensive experimental and clinical testing; and (4) hardware and software for a marketable, portable, dedicated ABR device will be developed.

Title of Project: Signal-Processing High-Frequency Audiometer
Principal Investigator: Robert A. Berkovitz
Awardee Organization: Audiometer Development Group
368 Common Street
Belmont, MA 02178
Telephone Number: (617) 489-1764/1765
Awardee Number: 2 R44 NS23285-02

A new high-frequency audiometer has been developed with NIH/NINCDS support. The audiometer uses digital signal processing to calibrate each ear individually and provides accurate estimates of the sound pressure level at the apex of the auditory canal. The new audiometer can serve in establishing valid audiometric standards for the normal population and for reliable determination of high-frequency hearing loss, an early warning of the long-term effects of exposure to excessive noise or ototoxic substances. Calibration is effected by analysis of features of the spectrum of an impulse reflected from the eardrum.

Audiometer Development Group plans to transform the present experimental prototype into a product that is compact, moderate in cost, and simple to use. Such a device would be responsive to the expressed needs of audiological clinics and of value in research aimed at discovery of ototoxic processes. Product development requires: detailed theoretical study of the acoustics of the ear canal, of the device, and of their interaction; design and construction of signal-processing circuitry suitable for quantity production; and, audiometric testing to validate each step of engineering design.

Title of Project: Voice-Pitch Tactile Display for the Deaf
Principal Investigator: David C. Coulter
Awardee Organization: Coulter Associates, Inc.
9613 Pembroke Place
Vienna, VA 22180
Telephone Number: (703) 698-0803
Awardee Number: 2 R44 NS22308-02

The goal of this project is to provide, in a marketable form, a sorely needed fundamental frequency (Fo) and prosody aid to deaf lip reading and speech production, based on adequate research and testing prior to design and packaging. To accomplish this goal, research programs at City University of New York and Gallaudet College will obtain basic cues on Fo perception, develop training curricula for deaf children in use of Fo information for reception and production, and conduct systematic observations of children using hardware developed in Phase I for fast start-up.

In a parallel effort, an all-digital implementation will be evaluated at Johns Hopkins University, using a sophisticated technique that makes use of a lip-reading corpus on laser disks, including electroglottograph recordings of the larynx. This system will help determine crucial design questions of single-channel versus multichannel stimulator presentation, scaling of Fo, and possible incorporation of feature detec-

tors to enhance lip reading or detect environmental sounds.

It is expected that the final version will employ digital implementation, giving far more flexibility both for improvement and use as a research tool than previous analog designs. If development is successful, Metavox, Inc. has agreed to manufacture and market the aid.

Title of Project: A Multichannel Wide-Band Biotelemetry System
Principal Investigator: Perry A. Mills
Awardee Organization: Data Sciences, Inc.
2678 Patton Road
Roseville, MN 55113
Telephone Number: (612) 636-0461
Awardee Number: 2 R44 NS23289-02

Data Sciences, Inc. proposes to develop and thoroughly test, *in vivo*, a commercially viable time-multiplex-based telemetry system suitable for short-range telemetry of biopotentials from animals as small as adult rats. This approach was chosen as a result of the Phase I effort involving a feasibility assessment of several alternate approaches based on market needs and engineering design considerations.

Data Sciences, Inc. will enhance the capabilities and miniaturize the transmitter prototyped in Phase I, develop a compatible receiver, and enhance existing data acquisition system capabilities to provide a complete system for telemetering and acquiring high-frequency biopotentials. This will be the first commercially available system to allow multichannel wireless monitoring of EEG, EMG, and single-unit potentials in small laboratory animals.

The system will allow laboratories involved in basic research, toxicological testing, and the evaluation of pharmaceutical compounds to collect data that are more definitive and less artifactual while using protocols that require fewer animals. Commercial markets for this device include academic, pharmaceutical, and government laboratories in addition to independent testing firms and chemical companies involved in the assessment of the toxic effects of chemicals.

Title of Project: Percutaneous Electrodes for Intramuscular Stimulation
Principal Investigator: Stuart F. Cogan
Awardee Organization: EIC Laboratories, Inc.
111 Downey Street
Norwood, MA 02062
Telephone Number: (617) 769-9450
Awardee Number: 2 R44 NS22738-02

A program to develop novel percutaneous electrodes for functional neuromuscular stimulation (FNS) is proposed. Neuromuscular stimulation requires small, flexible electrodes that can be inserted into individual muscles. Although the feasibility of restoring functional control has been demonstrated, the clinical use of FNS is limited, in part, by problems of electrode breakage, migration, and lack of specificity during stimulation. Three primary innovations for combating these limitations are proposed: (1) the introduction of a Ti-6Al-4V-ELI/Ta composite, a Ti-6Al-4V-ELI/Au composite, and tantalum as electrode-lead materials; (2) the introduction of IrO_2 and Ta_2O_5 as charge-injection materials; and (3) the introduction of Dacron velours and use of low-stiffness designs for preventing electrode migration.

Phase I demonstrated flexural fatigue resistance and compatibility with IrO_2 in the proposed lead materials. Phase II will involve the fabrication and characterization of complete FNS electrodes. Mechanical design techniques will be used to optimize electrode geometry for greater longevity. Physical characterization will include mechanical strength (tensile strength, ductility, etc.), fatigue life, microstructure, and lead impedance. Insulated electrode leads will be subjected to flexural fatigue, tensile, and corrosion tests. IrO_2 charge injection layers will be deposited thermally (TIROF) and by sputtering (SIROF) on optimized electrode leads. Cyclic voltammetry with short- and long-term *in vitro* pulsing tests will be used to characterize charge capacity, stability, and voltage transients.

Phase I Contracts

Title of Project: Automatic Enhancement of Clinical Evoked Potentials
Principal Investigator: Wallace E. Larimore, Ph.D.
Awardee Organization: Business and Technological Systems, Inc.
14504 Greenview Drive
Laurel, MD 20708
Telephone Number: (301) 470-3839
Awardee Number: 1 N43 NS72393-00

A variety of probes of brain function have been developed by clinicians and neuroscientists based on measurement of scalp-recorded electrical potentials evoked by specific stimuli, so-called evoked potentials (EPs). Signal enhancement of EPs is typically accomplished by ensemble averaging

In this Phase I study, automatic methods for greatly enhancing EPs are investigated, including the extraction of meaningful information from very few and even single EPs (sEPs). An initial study demonstrated considerable enhancement of transient phenomena, which have been inaccessible to averaging techniques, as well as great reduction in the time required to administer established EP measurements. For each stimulus presentation, a parametric model is estimated from prestimulus data, and poststimulus data are filtered using the model. The modeling method is a recently developed canonical variate analysis (CVA) of multivariate time series.

In the present study, a variety of stimulus paradigms are used, and the physiological validity of the enhanced EPs is evaluated. The enhancement technique is evaluated on data acquired for clinical assessment and for intraoperative monitoring, including the signal-to-noise enhancement and the required computation.

In Phase II, the signal enhancement computations will be optimized for real-time implementation on a microcomputer, and general purpose input/output routines will be developed to provide the broadest possible applicability of the method.

Title of Project: Magnetic Tactile Array
Principal Investigator: Edwin Langberg, Ph.D
Awardee Organization: Sensor Electronics, Inc.
105 Fairway Terrace
Mount Laurel, NJ 08054
Telephone Number: (609) 778-0850
Awardee Number: 1 N43 NS72394-00

For a multipoint tactile array system, two actuator designs are proposed: a magnetic and a PVdF design. The magnetic design is best suited for pin-to-pin spacing of 3 mm and larger. Pin travel amplitude of 2 mm (and longer if needed) can be readily implemented, and typical frequency response is adequate for the optimal 250 Hz frame-rate presentation. Floating pin suspension allows the pins to automatically conform to skin curvature. Actuators can be combined into modules, and a typical module consists of 8 × 8 actuators. The small and light array module is connected through a flexible 16-conductor cable to a control unit.

For ultradense arrays (0.5 mm to 3 mm pin-to-pin spacing), a PVdF design will be used. Pin travel amplitude is limited to a maximum of 30 microns. A very broad frequency response, exceeding by an order of magnitude the 0 to 400 Hz target, can be implemented. PVdF transducer technology lends itself to an actuator-driver integrated block (ADIB) design consisting of a row of 16 actuators with all logic and driver circuits integrated into one package. ADIBs are the basic building blocks; large arrays are created by stacking the individual blocks.

A proposed computer interface will allow an IBM PC-XT (or equivalent) to operate any array with 1,048, or possibly as many as 2,048, independently operated stimulator points.

Phase II Contracts

Title of Project: Time-Synchronized Parallel Data Collection and Processing
Principal Investigator: Richard J. Potash
Awardee Organization: Computer Sports Medicine, Inc.
21 Erie Street, #24
Cambridge, MA 02139
Telephone Number: (617) 354-3315
Awardee Number: 1 N44 NS72390-00

Medical monitoring involves the acquisition and processing of large amounts of raw data over long periods of time. Computer Sports Medicine, Inc. has developed a powerful data collection module with the ability for multiple modules to work in parallel, thus allowing the researcher to distribute the data processing tasks across a number of units.

Computer Sports Medicine, Inc. has implemented a prototype design and demonstrated the module's ability to communicate and execute sophisticated processing algorithms. In addition, the ability to provide real-time capture, storage, and display of test signals has been demonstrated.

The Phase II effort will concentrate on expanding the module's processing capabilities and developing a library of data acquisition algorithms.

Title of Project: A Statistics-Oriented Data Acquisition System
Principal Investigator: Eugene G. Merrill
Awardee Organization: SignifiCAn, Inc.
21 Main Street
Hudson, MA 01749
Telephone Number: (617) 562-7363
Awardee Number: 1 N44 NS72389-00

This proposal describes an automatic data acquisition system, constructed with multiple microprocessors, that emphasizes real-time assessment of deviation from the recent statistical history of simultaneously monitored signals. The system provides computerized graphics for representing these statistical trends for a multichannel system in real time. The system will compute averaged responses and event histograms, each with corresponding point-for-point variance waveforms. Data streams will be reduced to moving statistical profiles and will be stored in formatted digital files.

This system will have direct application in the recording, reduction, and analysis of the large quantities of data collected during long-term clinical/physiological monitoring.

DIVISION OF RESEARCH RESOURCES

Phase I Grants

Title of Project: Development and Testing of Laminar Flow Isolators for Rodent Colonies
Principal Investigator: Kenneth Abel
Awardee Organization: The ABEL Company
State Route 774, Box 267
Pembroke, VA 24136
Telephone Number: (703) 626-3036
Awardee Number: 1 R43 RR03564-01A1

The specific aim of this study is to design and evaluate the use of HEPA-filtered, laminar flow isolation systems as substitutes for present barrier systems in germ-free and gnotobiotic research using rodents and other small animals.

Title of Project: Monoclonal Antibodies Against the MHC of Inbred Rats
Principal Investigator: Harold A. Hoffman, Ph.D.
Awardee Organization: Animal Genetic Systems, Inc.
628-G Lofstrand Lane
Rockville, MD 20850
Telephone Number: (301) 251-1101
Awardee Number: 1 R43 RR03542-01

The objectives of this proposal are to: (1) produce allotypic monoclonal antibodies that distinguish class I and class II antigens coded by the RT1 loci major histocompatibility complex (MHC) in the laboratory rat, and (2) characterize the anti-MHC monoclonal antibodies by biochemical and genetic methods to determine their antigenic specificity for class I and class II antigens of different MHC haplotypes using 11 strains of inbred rats. The antibodies will be used in combination with other procedures for genetic definition within the MHC.

Phase I research included induction and characterization of allotypic monoclonal antibodies against the 10 known haplotypes of the rat MHC. Phase II will include production and characterization of monoclonal antibodies against the 10 known haplotypes of the rat MHC.

Title of Project: Development of a PC-Based System for Electron Microscopes
Principal Investigator: Richard J. Lee, Ph.D.
Awardee Organization: Atmospheric Research Organization, Inc.
Energy Technology Consultants
350 Hochberg Road
Monroeville, PA 15146
Telephone Number: (412) 325-1776
Awardee Number: 1 R43 RR03556-01

It is proposed that a personal computer (PC)-based system be developed that will provide a cost-effective method for collecting, processing, and analyzing image data in electron microscopes. Widespread use of this technology for health and biomedical research would be feasible if less expensive instrumentation were available.

A PC-based system is needed because the practical utility of currently available electron-microscope-image analysis systems is limited due to the cost and complexity of available instrumentation. This instrumentation is of value because image analysis and processing techniques can resolve subtle composition differences that are not readily apparent in the electron microscope image or micrograph. Thus, subtle differences due to the effects of external agents can be qualified and quantified.

The key technical innovation and goal of this project will be to design an interface permitting the use of currently available, general-purpose personal computers. Efforts derived in the Phase I program will explore the feasibility of developing a prototype PC-based system. Continued development of this system in Phase II and beyond will result in a low-cost system for collecting, processing, and analyzing images that successfully integrates PC technology with electron microscopy.

Title of Project: Subpicosecond Desorption and Mass Analysis of Large Molecules
Principal Investigator: Larry J. Moore
Awardee Organization: Atom Sciences, Inc.
114 Ridgeway Center
Oak Ridge, TN 37830
Telephone Number: (615) 483-1113
Awardee Number: 1 R43 RR03533-01

Emerging health and medical research problems are placing stringent requirements on the ability to characterize labile and high-molecular-weight organic compounds. In biotechnology, for example, intermediate synthesis products must be identified. Recent ion bombardment desorption models suggest that highest-molecular-weight compounds would desorb most efficiently through rapid, multiple excitations near the molecular attachment site. Resonance ionization spectroscopy has the potential to deliver spatially constrained primary ion bundles on target in the picosecond range. The successive ion arrival-time intervals for this source are commensurate with subpicosecond times theoretically predicted for molecular motic and energy transfer to the attachment site.

The specific aims of this proposal are to: (1) modify a thermal atomization source and ion-extraction lens for a primary resonance-ionization bombardment source; (2) modify an existing time-of-flight mass spectrometer for higher resolution; (3) evaluate the temporal width of the primary ion pulse; and (4) investigate the feasibility of efficient desorption of very high-molecular-weight species. The potential multiple excitation efficiency and temporal resolution of the proposed source would simultaneously provide the basis for desorption of very high-molecular-weight molecules and for an ultrahigh-resolution, time-of-flight mass spectrometer.

Title of Project: Miniaturized Raman Clinical Gas Analyzer
Principal Investigator: Richard A. Van Wagenen, Ph.D.
Awardee Organization: Biomaterials International, Inc.
420 Chipeta Way, Suite 160
Salt Lake City, UT 84108
Telephone Number: (801) 583-8444
Awardee Number: 1 R43 RR03863-01

A need exists to quantitate anesthetic and respiratory gases (O_2, CO_2, N_2) in the operating room. Previous work has shown that Raman light scattering can be successfully utilized for molecular gas analysis. The Raman signal for each gas can be separated from the laser beam Rayleigh scatter via filter combinations, thus eliminating the need for large, expensive monochromators.

This proposal addresses the feasibility of utilizing a small, light, intracavity, frequency-doubled, diode-pumped Nd:YAG laser as an alternative to the large, inefficient Ar^+ laser used in previous work. A research prototype will be constructed that uses such a commercially available solid-state laser. A multichannel gas cell will be inserted into an intracavity space, which will be pumped by this laser. The Raman signal intensity will be determined for the above noted gases and compared to the values calculated from a system-modeling equation. Accuracy, sensitivity, specificity, and linearity will also be evaluated for each gas. Should this approach prove feasible, the use of such a laser would greatly reduce instrument size, weight, and cost, thus making it more widely available to the anesthesiology community.

Title of Project: Isogenic Amphibians for Biomedical Research
Principal Investigator: Ann Janice Brothers, Ph.D.
Awardee Organization: Central Valley Biological, Inc.
112 Burch Drive
Yerington, NV 89447
Telephone Number: (702) 784-6136
Awardee Number: 1 R43 RR03804-01

Recently, considerable progress in the genetic and molecular analyses of development has been obtained. There are powerful new molecular techniques that can be applied to analyze those genes important in the regulation of development; however, those techniques must be used with genetically defined research animals. Isogenic lines are available in the mouse and drosophila, but are not available in the amphibian. The research presented in this proposal focuses on the development of clonal isogenic stocks of the amphibians, *Xenopus laevis* and *Ambystoma mexicanum*. The availability of such stocks would provide research materials of tremendous value to the biomedical research community.

Title of Project: A Single-Chip Processor for Tomographic Reconstruction
Principal Investigator: Michael E. Casey
Awardee Organization: Computer Technology and Imaging, Inc.
810 Innovation Drive
Knoxville, TN 37922
Telephone Number: (615) 966-7539
Awardee Number: 1 R43 RR03541-01

A single-chip engine for tomographic reconstruction is proposed by Computer Technology and Imaging, Inc. The engine would be fabricated using current VLSI technology. Such an engine can be replicated and used to implement a reconstruction processor. A processor using just eight of the VLSI engines could have a price/performance enhancement over current commercial reconstruction processors of a factor of 25.

The investigation will focus on the verification of the engine with computer and hardware simulation, as well as the feasibility of implementing the engine as a VLSI device.

Title of Project: An Analytical Database Management System for Geneticists
Principal Investigator: Elizabeth A. Thompson, Ph.D.
Awardee Organization: DMS Systems, Inc.
1111 Brickyard Road
Salt Lake City, UT 84106
Telephone Number: (801) 484-3333
Awardee Number: 1 R43 RR03678-01

The goal of this proposal is to produce an analytical database system for geneticists to facilitate the task of collecting, organizing, and maintaining data specific to this field. Many disparate programs are available for the analysis of genetic data, but most require computing and genetic analysis expertise for their use, and all require the geneticist to direct the analysis strategy appropriately. Each program has different data requirements.

To facilitate genetic research, DMS Systems, Inc. has devised special utilities in the GENISYS database management system for storing and retrieving familial data. This software will be interfaced with analysis programs to allow pedigree manipulation and analysis functions to be called directly from the database system. An expert system will also be interfaced to the database system so that the system can use predetermined strategies to guide the collection and analysis of data.

The integration of a database management system with genetic utilities, an expert system, and analytical programs will create a new tool of wide applicability. This tool will be of considerable interest in institutions focused on molecular genetics, clinical genetics, and/or genetic analysis. It will have broader application as these technologies become standard diagnostic and predictive procedures in hospitals, HMOs, and physicians' offices.

Title of Project: Development of a Scientific Summary Language – MEDLISH
Principal Investigator: David S. Becker, Ph.D.
Awardee Organization: I. S. Grupe
948 Springer Drive
Lombard, IL 60148
Telephone Number: (312) 627-0550
Awardee Number: 1 R43 RR03572-01

Current scientific bibliographic databases (e.g., MEDLINE) now play a central role in literature activities. They are important and they are widely used. However, the information expressed in the *TITLE*, *ABSTRACT*, and *MeSH INDEX* fields in these databases is quite chaotic and sketchy compared with the structure of many other kinds of databases. Because of these deficiencies, computerized literature searches are imprecise and merely retrieve records based on the presence of "keywords," rather than via a precise "match on concept" condition, such as is possible with relational databases and other orderly data structures.

In this Phase I program, I.S. Grupe (ISG) proposes to make a small database containing the kind of information that is in ordinary abstracts, but to express it in a new "scientific" language (MEDLISH) that ISG has been developing. Unlike English, MEDLISH enforces order, scientific precision, and logic on the entries.

At the conclusion of Phase I, the design will have been completed, a sample database made, and the implementation plans finished. In Phase II, ISG will attempt to make the product marketable. A database expressed in MEDLISH will support much more precise queries than current bibliographic databases.

Title of Project: Fibrous Substrates for Cell Culture
Principal Investigator: Eric M. Simon
Awardee Organization: IMW Acquisition Company, Inc.
274 South 1200 East
Salt Lake City, UT 84102
Telephone Number: (801) 581-6499
Awardee Number: 1 R43 RR03544-01

The aim of this proposal is to investigate the tissue-growth enhancement capabilities of fibrous polymeric substrates produced by a novel technique. This technique is capable of producing geometrically defined, nonwoven mats composed of 0.1 to 1.0μ diameter fibrils. Unlike conventional fibrillation techniques, the proposed technique can utilize a large variety of polymeric solutions as the fibrillation medium and is able to induce polar molecular enrichment on the fibril surface. It is our intent to investigate the use of a "disc insert" configuration, i.e., the fibrous substrate will be configured into a disc of the proper proportions such that it can readily be placed into an untreated vessel. This configuration would not only enhance cell growth but also reduce costs and increase ease of postculture characterization.

The goal in Phase I is to complete the fibrillation device, produce the fibrous substrates, culture cells on these substrates, and interpret the results. Four parameters will be varied: substrate material, fibril diameter surface polarity, postfibrillation treatment, and type of cell cultured. Characterization techniques will include ESCA, SIMS, light and electron microscopy, and morphological studies.

In Phase II, additional materials and parameters will be investigated, work on scaling-up the fibrillation device will be initiated, and associated *in vitro* and *in vivo* studies performed.

Title of Project: Adaptation of ELISA/IFAT for Serodiagnosis of Tyzzer's Disease
Principal Investigator: Robert L. Peters, Ph.D.
Awardee Organization: Microbiological Associates, Inc.
9900 Blackwell Road
Rockville, MD 20850
Telephone Number: (301) 738-1000
Awardee Number: 1 R43 RR03805-01

Microbiologically defined laboratory animals are required for sophisticated biomedical research. Serological procedures are the most feasible and economical means to monitor their health status. Tyzzer's disease is one of the more insidious diseases of laboratory rodents and rabbits for which a serologic test procedure is not available commercially. The elusive fastidious etiologic agent, *Bacillus piliformis* (Tyzzer), is a gram-negative, spore-forming, flagellated, obligate intracellular parasite that remains unclassified. Typical histopathology forms the basis for diagnosis in 18 animal species. Immunosuppression precipitates clinical disease, and transmission occurs vertically as well as horizontally. Serological surveys in Japan and Europe indicate that inapparent infections are common in cesarean-derived, barrier-maintained colonies of rats.

Microbiological Associates, Inc. proposes to prepare seed pools of three strains of *B. piliformis* (propagated in embryonated eggs and 3T3 cell cultures), prepare antisera to each strain in mice, adapt the ELISA and IFAT techniques for serodiagnosis, determine the degree of antigenic relatedness between strains, and provide serodiagnostic services to the biomedical research community at reasonable cost.

Title of Project: Chemical Equilibrium Software Development
Principal Investigator: Myles L. Lamson, Ph.D.
Awardee Organization: MicroMath Scientific Software, Inc.
2034 East Fort Union Boulevard
Salt Lake City, UT 84121-3144
Telephone Number: (801) 942-1011
Awardee Number: 1 R43 RR03565-01

A wide range of individuals in health-related professions (e.g., pharmaceutics, medicine, biology, and medical research) frequently have a need to prepare standard aqueous solutions of various buffers, possibly in the presence of metal ions, or to calculate certain solution parameters from other known quantities. These calculations are often rough approximations. A complete model of even relatively simple aqueous buffer solutions may require the use of complicated iterative numerical techniques in order to simultaneously solve dissociation equilibria, complex formation equilibria, and equilibrium with a solid phase. Concurrently, appropriate activity coefficients must be determined.

The long-term objective of this project is to develop comprehensive software tools that will enable researchers in health, science, and other fields to formulate and evaluate complicated solution equilibrium models in a timely and precise manner. The software package to be developed will allow users to specify solution properties such as pH, buffer capacity, etc.; the software will then search a database for the appropriate solution reactions and equilibrium constants and calculate specified output.

Title of Project: Inversion of Laplace Transforms on Microcomputers
Principal Investigator: Myles L. Lamson, Ph.D.
Awardee Organization: MicroMath Scientific Software, Inc.
2034 East Fort Union Boulevard
Salt Lake City, UT 84121-3144
Telephone Number: (801) 943-0290
Awardee Number: 1 R43 RR03810-01

The application of physical-chemical principles to biological systems frequently leads to situations in which the quantitative treatment of conceptually simple models is confounded by the complexity of the system. Such is the case, for example, in the study of the permeation (and possible concurrent metabolism) of drugs through complex biological membranes, the physiological modeling of the distribution of drugs throughout the body, and the treatment of flow of fluids and concurrent diffusion/metabolism.

Each of these problems can be approached by the technique of Laplace transforms and expressions readily developed for the Laplace transform of the problem's solution. The inversion of the Laplace transform to recover the problem solution is often sufficiently difficult to preclude the use of this otherwise elegant technique.

The aim of this project is to utilize a recently published algorithm for the reliable and accurate numerical inversion of the Laplace transform as a building block for the development of an interactive and easy-to-use microcomputer program for the inversion of Laplace transforms. Problems that now take a day or more to solve by hand will be solved in seconds or minutes, complete with appropriate graphical output of results. The Laplace transform will assume the role of a routine everyday tool, rather than remain a curiosity that, for many scientists, is of little practical worth.

Title of Project: Placement Resource System
Principal Investigator: Michael Gorodezky, Ph.D.
Awardee Organization: Poolman, Shih & Platton, Inc.
1182 Market Street, Suite 216
San Francisco, CA 94102
Telephone Number: (415) 626-9436
Awardee Number: 1 R43 RR03539-01

This project will test and evaluate the feasibility of an online discharge-planning resource system listing information on nursing home providers. The system will provide automated retrieval capabilities to hospital-based discharge planners, who will be able to identify discharge placement alternatives with greater efficiency. The system will permit discharge planners to have immediate access to information regarding nursing home facilities. Bed availability as well as facility characteristics will be maintained online. Techniques for updating and maintaining this database of information that is constantly changing will be studied and evaluated.

The placement resource system will be a commercially viable product. Acute-care hospitals will benefit from the system, as it will help promote more timely and appropriate discharge to nonacute settings. A reduction in unnecessary acute hospital days will directly benefit hospitals under prospective payment reimbursement formulas. Nursing homes will benefit from a system that will immediately notify hospitals of available nursing home beds.

Title of Project: A Low-Cost, Laser-Disk, Image Database System
Principal Investigator: Ruth E. Dayhoff, M.D.
Awardee Organization: Potomac Medical Systems
P.O. Box 4212
Silver Spring, MD 20904
Telephone Number: (202) 625-2121
Awardee Number: 1 R43 RR03569-01

Potomac Medical Systems proposes to design and produce a low-cost, medical image database system. The system would be built around off-the-shelf, low-cost components, many of which are already in place in the target institutions. The images would be stored on removable write-once, laser-based, optical disks.

The inability to conveniently store and retrieve large numbers of images represents a long-standing problem in medical fields utilizing images for their work. The advent of reasonably priced optical disks offers the possibility of bringing the benefits of computerization to various areas of medical research and education, including pathology, radiology, nuclear medicine, and physical diagnosis.

Image database systems have the potential to revolutionize medical research, education, and clinical care. Such systems would facilitate image examination and analysis, integration of images with other database information, and research and teaching by analyzing complete data in a fashion not previously available.

Title of Project: True-Color Image Workstation for Pathology Research
Principal Investigator: Ruth E. Dayhoff, M.D.
Awardee Organization: Potomac Medical Systems
P.O. Box 4212
Silver Spring, MD 20904
Telephone Number: (202) 625-2121
Awardee Number: 1 R43 RR03801-01

Until now, the benefits of computerization have not spread to image-based fields such as pathology. Although a few expensive image-processing computer systems have been used for pathology research, affordable, general-purpose systems have been unavailable. Image processing has been limited to black-and-white images. Recent progress in microcomputer image-processing hardware will now allow the production of affordable systems that provide true-color image processing and sophisticated image storage and retrieval systems.

The aim of Phase I of this project is to design a true-color image-processing workstation for pathology research. The workstation will be based on a powerful microcomputer, specialized off-the-shelf hardware to obtain true-color microscopic images, and a removable write-once laser disk drive to provide high-capacity storage for images. Image-processing software will be designed to allow routine image measurement, manipulation, identification, and analysis. Research will be done on algorithms for true-color image processing, and a storage and retrieval system for images will be planned. Finally, all system components will be integrated into a user-friendly research environment.

Phase II of this project will include assembly of the workstation, development of image-processing software, testing, and field trials.

Title of Project: Laser Microsurgery System
Principal Investigator: C.P. Christensen, Ph.D.
Awardee Organization: Potomac Photonics, Inc.
University of Maryland, Building 335
College Park, MD 20742
Telephone Number: (301) 454-4973
Awardee Number: 1 R43 RR03676-01

Construction and characterization of an advanced microsurgical system is proposed. The system utilizes a pulsed, high-repetition-rate ultraviolet excimer laser to carry out tissue removal with very high spatial resolution and minimal thermal damage. The apparatus incorporates sensitive optical sensors capable of detecting color, fluorescence spectra, or spatial features of tissue of interest. A novel feedback control uses sensor data to allow removal of only specific types of tissue and to improve precision in microsurgical processes.

Title of Project: Software for Analysis of Incomplete Longitudinal Data
Principal Investigator: M.W. Helms
Awardee Organization: Rho, Inc.
102 Hunter's Ridge Road
Chapel Hill, NC 27514
Telephone Number: (919) 933-2540
Awardee Number: 1 R43 RR03552-01

Medical research frequently involves longitudinal and/or multivariate measurements; when the research involves humans or laboratory animals, the data are often incomplete or involve time-dependent covariates, problems that traditional statistical techniques and software cannot handle properly. Many important advances have been made in statistical methods for incomplete longitudinal/multivariate data in the past 5 to 10 years, but these methods are not generally available to medical researchers due to a lack of high-quality, user-friendly computer software.

The ultimate goals of this project, including Phase II, are to produce and market such software for use on mainframes and large microcomputers. The software will implement methods for linear models with linear covariance structure, subject to linear constraints, which have been shown to be extremely useful for analysis of incomplete medical research data. Phase I will include research to: (1) select algorithms for the fundamental computations; (2) design overall program structure; (3) design two user interfaces (menu and command-language driven) for each

program; and (4) implement, debug, test, and document prototype software. Phase II will include: (1) research with the prototype software to improve user interfaces and program performance and (2) development of highly efficient, user-friendly production software which will be marketed.

Title of Project: Removal of Distortion from Magnetic Resonance Images
Principal Investigator: Douglas A. Greer
Awardee Organization: SAM Technology, Inc.
1855 Folsom Street
San Francisco, CA 94103
Telephone Number: (415) 621-3999
Awardee Number: 1 R43 RR03553-01

While Magnetic Resonance Image (MRI) scans are invaluable because of their high degree of anatomical differentiation and their lack of ionizing radiation, they contain an inherent nonlinear distortion that can exceed 15 percent. Existence of this distortion has not been well documented by MRI device manufacturers, and without distortion compensation, quantitative MRI measurements such as position, length, area, and volume are erroneous.

Using a generic graphics software system, SAM Technology, Inc. developed, in connection with basic research on functional neuroanatomical correlations, a program for manipulating MRI data. A feasibility study to determine whether and how phantom calibration data and data from a registration cap to be worn by patients can be used to correct the distortion in MRIs will be performed. If the Phase I effort is successful, in Phase II this software will be generalized into a portable, low-cost set of tools that researchers and clinicians could use to correct, enhance, and quantitatively measure their MRI data.

Title of Project: Computer-Controlled Electrophysiological Instruments
Principal Investigator: Charles W. Scouten, Ph.D.
Awardee Organization: Stoelting Company
1350 South Kostner Avenue
Chicago, IL 60623-1198
Telephone Number: (312) 522-4500
Awardee Number: 1 R43 RR03531-01

A laboratory automation system (LAS) for electrophysiologists will be developed. It will consist of a computer-controlled network of nine smart instruments, which would replace their conventional counterparts, including a stimulator/controller, analog and digital switching devices, waveform generator, physiological monitor, interval analysis system, waveform processor (averager), electrometer, and waveform recognition device. Appropriate ancillary devices will also be developed. The LAS will provide automation of difficult and time-constrained experiments, with the eventual addition of expert system supervision.

In Phase I, development of the devices already begun will continue, and development of more sophisticated devices will begin. In Phase II, the development of the proposed devices will be concluded. These devices can be used in electrophysiological research, i.e., in studies of neurophysiological mechanisms of normal and pathological processes. Some devices, such as the physiological monitor, can be used for monitoring subjects' physiological states, e.g., during sleep studies.

Title of Project: Expert System Development of a Clinical Record System
Principal Investigator: Ben T. Williams, M.D.
Awardee Organization: University Park Pathology Associates, P.C.
1408 West University Avenue
Urbana, IL 61801
Telephone Number: (217) 337-2175
Awardee Number: 1 R43 RR03557-01

Beginning over a decade ago, University Park Pathology Associates, P.C. developed a basic comprehensive computer-based record system for ambulatory care. The system capitalizes on the touch-interactive graphic capabilities of the PLATO computer-aided instruction system of the University of Illinois. Although impressive performance was achieved in evaluation, the development environment was not suited to deployment at sites of care.

This proposal is to use expert system capabilities to transfer and refine the original system. When acceptable performance, in terms of flexibility, comprehensiveness, and speed and facility of interaction have been achieved in the development environment, the system will be moved to stand-alone and/or networked terminals of the personal computer class.

Successful development of an economically realistic system will achieve a long-elusive objective for the support of clinical care. Secondary benefits include making it easier for the practitioner to access decision support tools and the development of machine-manipulable databases for clinical research and quality assurance.

Title of Project: Development of a High-Resolution Image Display System
Principal Investigator: Philip Spitler
Awardee Organization: Xinix, Inc.
3745 Chatham Road
Ellicott City, MD 21043
Telephone Number: (301) 465-3652
Awardee Number: 1 R43 RR03562-01

Xinix, Inc. has completed a schematic-level electronic design for a high-quality, low-cost display system for analysis of medical images from CT scanners, MR scanners, and digital radiography devices. The system will be able to transmit and receive digital images over telephone lines and will include a 1,280 by 1,024 black and white CRT display with 250 assignable gray levels.

It should be possible to build such a system and sell it profitably for $20,000 to $25,000. At this price level, systems can be economically installed at remote radiology offices so that images can be analyzed using displays that are of comparable quality and similar function to those of the imaging system. This should improve the responsiveness and accuracy of remote image analysis versus the use of messenger-carried film. Reduction in the need for radiologist travel to perform analysis may also reduce costs. The requested Phase I grant is to be used for the building and testing of one prototype system.

Phase II Grants

Title of Project: Raman Scattering for Clinical Gas Diagnosis
Principal Investigator: Richard A. Van Wagenen, Ph.D.
Awardee Organization: Biomaterials International, Inc.
420 Chipeta Way, Suite 160
Salt Lake City, UT 84108
Telephone Number: (801) 583-8444
Awardee Number: 2 P44 RR02613-02

Quantification of a number of molecular gases is required in clinical environments. These include respiratory and anesthetic gases, blood pO_2 and pCO_2, the toxic trace gases (e.g., ethylene oxide, formaldehyde), escaped anesthetic agents, and gases used for noninvasive lung function and cardiac output determinations. Raman light scattering provides a means of detecting and quantifying such gases.

The development of a multichannel prototype instrument to detect respiratory and anesthetic gases in the operating room is addressed in this research. The prototype utilizes an Ar^+ laser as the scattering source and a microprocessor for signal counting, data processing, and display control. The gas sample is oriented in the intracavity of a laser for enhanced optical power. Laser, optics, and detector innovations are proposed which should extend sensitivity to the ppm level. Multichannel monitoring of the entire Raman spectra for better resolution is also addressed via the evaluation of suitable spectral dispersive elements and light detectors. The prototype's applicability to monitor respiratory and anesthetic gases will be evaluated. Such a prototype bridges the gap between the previous fundamental research and preproduction designs.

Title of Project: Enzyme-DNA Conjugates for Direct Detection of DNA Hybrids
Principal Investigator: Edward G. Jablonski, Ph.D.
Awardee Organization: Molecular Biosystems, Inc.
11180-A Roselle Street
San Diego, CA 92121
Telephone Number: (619) 452-0681
Awardee Number: 2 R44 RR03105-02

The goal of this project is to develop and optimize a direct, nonradiometric DNA hybridization detection system based upon the novel formation of sequence-specific, chemically synthesized oligonucleotide probes covalently linked to alkaline phosphatase. The long-term objective is to deliver to the clinical market a rapid, sensitive, and automated system for the determination of specific bacteria, virus, and genetic abnormalities whose identification by current immunoassay or culture technology is difficult or laborious.

Specifically, the production of current and new oligomer-enzyme conjugates will be optimized. Conditions for maintaining stability and maximum enzyme activity under storage, hybridization, and assay conditions will be identified. The use of fluorogenic substrates for increased sensitivity and automation compatibility will be explored. Hybridization systems using filter membranes, bead solid supports, or solutions will be developed using conjugate detection. Trials will be conducted with the conjugates for detecting viral and bacterial DNA in clinical samples, with the goal of marketing specific detection kits for various pathogens.

Title of Project: 4.7 Tesla 500-mm Bore Superconductive NMR Imaging Magnet
Principal Investigator: James L. Carolan, Ph.D.
Awardee Organization: Nalorac Cryogenics Corporation
637 Arnold Drive, Suite 600
Martinez, CA 94553
Telephone Number: (415) 229-3501
Awardee Number: 2 R44 RR02612-02

The short-term goal of this project is the development of a high-resolution 4.7 Tesla 500-mm-diameter, room temperature, bore superconductive nuclear magnetic resonance (NMR) imaging magnet system for *in vivo* biochemical NMR studies. The high field, large bore, and high homogeneity of the proposed magnet system will provide the facility for *in vivo* NMR study with less abundant nuclei of moderate size animals and pediatric patients.

In Phase I, a detailed design was developed for the magnet system blending methods and technology developed at Nalorac Cryogenics Corporation (NCC) with techniques developed at Lawrence Berkeley Laboratory (LBL). The magnet will be internally shielded for stray magnetic fields outside the bore and will be housed in a cryogenic vessel that will permit operation for in excess of one-half year without liquid helium refill. The combination of NCC's experience with commercial production of high-resolution superconductive magnets and LBL's experience with design and construction of large, high-stored energy superconductive magnets significantly enhances the probability of full success of Phase II. The long-range goal of the project is to provide the expertise to pursue internal development of a wide range of high-resolution superconductive magnets including wide bore horizontal magnets.

Title of Project: Tongue-Activated Communication Control for the Disabled
Principal Investigator: Daniel Fortune
Awardee Organization: Zofcom, Inc.
1895 Oak Knoll Lane, #20A
Menlo Park, CA 94025
Telephone Number: (415) 854-3449
Awardee Number: 9 R44 RR04354-02

A tongue-activated intraoral communications controller permits paraplegics and quadriplegics rapid computer input and device operation. Since tongue function closely resembles the fingers in sensitivity, quickness, and spatial awareness, the tongue is an ideal means of communication.

This research project will further develop a device controller that offers significant advantages over existing controllers for the severely disabled. Zofcom, Inc. has developed a Tongue-Activated Communications Controller (TACC) that utilizes microprocessor technology and biotelemetry techniques to control personal computers and related equipment.

The flexibility of the TACC for a broad spectrum of commercial applications will give disabled people with limited mobility the opportunity to perform normal daily activities and develop new educational and employment skills.

The feasibility of integrating a wireless tongue-activated transmitter into a removable dental retainer and interfacing this device with a personal computer was demonstrated in Phase I. During Phase II, clinical testing and evaluation will be undertaken to further refine and develop the TACC into a commercially viable product.

NATIONAL CENTER FOR NURSING RESEARCH

Phase I Grant

Title of Project: Information System for Patient Self-Care
Principal Investigator: Patricia Ann Sayers
Awardee Organization: Nursing Systems International, Inc.
2050 Cedar Lane, RD #1
Bordentown, NJ 08505
Telephone Number: (609) 499-3916
Awardee Number: 1 R43 NR01845-01

Orem's Self-Care Nursing Model is the most widely applied nursing model in clinical use today. In this model, departmental activities, as well as patient care outcomes, are linked at all levels. Through use of Orem's language, common measurable goals and consistency in desirable patient outcomes, nurse productivity can be described in reference to patient care outcomes.

The research proposed is to develop an application of the Orem Self-Care Nursing Model for IBM PC-compatible computers. During Phase I, the following will be selected for use: data-gathering tools for patient care assessment, administration of nursing care, and patient outcomes; work-flow plan for a computer-assisted assessment and care system; and testing methodology for verification of patient assessment and measurement of patient outcomes. In addition, clinical testing sites will be identified.

Phase I Grant

Title of Project: Alcohol Detection Device
Principal Investigator: Mervin J. Moldowan
Awardee Organization: Moldowan Laboratories, Inc.
P.O. Box 788
Philomath, OR 97370
Telephone Number: (503) 929-2455
Awardee Number: 1 R43 AA07174-01

The purpose of this project is to develop a noninvasive alcohol-detecting device to be used by people who are not trained in chemistry. The basis for alcohol detection is the use of alcohol oxidase to metabolize ethanol and a chromogen peroxidase system for hydrogen peroxide analysis. Components in saliva are to be examined for their potential interaction with the alcohol oxidase-peroxidase system. This technology was developed in earlier research, but requires further improvement and refinement. Improvements will include vivid color shades at critical ethanol levels.

Phase II Grants

Title of Project. Accurate Alcohol Breath Testing
Principal Investigator: Mary Ann Mandelkorn
Awardee Organization: Meridian Medical Corporation
5025 25th Avenue NE, Suite 204
Seattle, WA 98105
Telephone Number: (206) 522-8922
Awardee Number: 2 R44 AA06881-02

Meridian Medical Corporation proposes to develop and test a breath sample system that will increase the breath alcohol test accuracy from -50% to ±6% when attached to commercially available breath test devices. The sample system will use the isothermal rebreathing technology already developed to eliminate the physiological errors associated with current systems In its Phase I work, Meridian confirmed that errors could be reduced to this extent while retaining the same ease of use found in current commercial units.

During the proposed two-year Phase II, a preproduction prototype sample system will be designed, fabricated, laboratory-tested on humans, field-tested by law enforcement personnel, and submitted to the federal Department of Transportation for approval.

Title of Project: Use of Autotimer in Alcohol/Drug Rehabilitation
Principal Investigator: William B. Leaf
Awardee Organization: Prototypes, Inc.
10449 Metropolitan Avenue
Kensington, MD 20895
Telephone Number: (301) 942-1731
Awardee Number: 2 R44 AA06523-02

Phase I involved the development and road test of a prototype Autotimer. This is a device that records unauthorized driving by a suspended drunk driver who has been granted permission by the court to drive to and from work.

Phase II will include a large-scale field test of the Autotimer. In this field test, the court will provide individuals whose licenses are suspended with the opportunity to have the Autotimer device installed in their vehicles. Those that accept this opportunity will pay an installation and monitoring fee for the 6-month suspension period. In the course of the evaluation, approximately 1,000 offenders will be provided with the Autotimer. Their driving records during the suspension period and for a period of 1 year following the end of suspension will be compared with offenders who are suspended or who received limited licenses without the requirement of a monitoring device. The objective of the Phase II field test is to demonstrate that the Autotimer will reduce alcohol-related accidents of convicted drunk drivers.

NATIONAL INSTITUTE ON DRUG ABUSE

Phase I Grants

Title of Project: Training Media Regarding Mentally Ill Substance Abusers
Principal Investigator: Vivian B. Brown, Ph.D.
Awardee Organization: B&B Management Research
822 Sixth Street
Manhattan Beach, CA 90266
Telephone Number: (213) 379-0732
Awardee Number: 1 R43 DA04250-01A1

B&B Management Research proposes to determine the feasibility of developing and marketing two multimedia training packages for the assessment, diagnosis, and treatment of mentally ill substance abusers. One training package will be designed for drug and alcohol treatment providers and the other for mental health treatment proivders. The proposed work includes gathering technical information about training package contents and formats, and preparing market and production-cost analyses. Information will be gathered through interviews, literature reviews, use of both professional and business development advisory committees, and a small learning conference.

A final report will present detailed technical, market, and cost analyses, and will include conclusions regarding potential for development and marketing of the training packages and, if warranted, a proposal for such development under Phase II SBIR funding.

Title of Project: Enzyme-Linked Immunosorbent Assay for Cotinine
Principal Investigator: Roger N. Piasio
Awardee Organization: Binax, Inc.
95 Darling Avenue
South Portland, ME 04106
Telephone Number: (207) 772-3544
Awardee Number: 1 R43 DA05387-01

The long-term objective of the proposed work is to provide physicians and others in the field of preventive health care delivery with an inexpensive and reliable biochemical test to measure patients' exposure to tobacco smoke. At present, a reliable test of this type is not available on a commercial basis. Cotinine, a metabolite of nicotine, has been selected as the product to measure because of its chemical stability, specificity as a marker, and relatively long circulating half-life. Having access to this test will enhance the process of smoking abatement, whether gradual reduction techniques (e.g., nicotine fading) or abrupt withdrawal are employed, and the test can also be employed to emphasize to patients that tobacco smoke products are actually being absorbed into the system.

As a first step, an enzyme-linked immunosorbent assay (ELISA) will be developed to measure cotinine; it will be capable of assessing qualitatively the extent of tobacco smoke exposure in saliva and/or urine. Binax, Inc. intends to take advantage of a recent advance in producing polyclonal cotinine antisera that allows for selective removal of "bridge" antibodies that have, in the past, produced high backgrounds and diminished sensitivity. To achieve a detection limit of 10 ng/ml, the cotinine level that separates smokers from nonsmokers, it is proposed to use a simultaneous solid-phase competitive inhibition assay in which binding of enzyme-labeled cotinine antibody to immobilized cotinine is competitively inhibited by cotinine present in the patient sample. In Phase II, Binax, Inc. proposes to carry out a field trial of the test.

Title of Project: Rapid Enzyme Immunoassay for Cannabinoids in Blood
Principal Investigator: Peter H. Duquette, Ph.D.
Awardee Organization: Bio-Metric Systems, Inc.
9932 West 74th Street
Eden Prairie, MN 55344
Telephone Number: (612) 829-2714
Awardee Number: 1 R43 DA04463-01

Serious attention has been focused on the use of illicit drugs by Americans in all walks of life. One of the most abused drugs for over two decades has been marijuana, which is now being used by blue- and white-collar workers, military personnel, professional athletes, and high school students. Because of this, many employers (including the U.S. military) are beginning to demand that workers suspected of drug use undergo drug testing.

A variety of methods are available for specific and sensitive determination of marijuana and its major metabolites in biological fluids. Most available assays (e.g., HPLC, GC-MS) require expensive equipment, trained personnel, and are slow to determine cannabinoid use.

Bio-Metric Systems, Inc. proposes to develop an enzyme immunoassay (EIA) that will be useful for the detection of low concentrations of the major cannabinoids in blood. Blood obtained by a fingerprick can be analyzed directly by the assay, thus eliminating possible sample contamination. This qualitative assay would serve as an excellent screen for possible cannabinoid abuse, but all positive samples would require verification by more sensitive and quantitative assays. The assay is simple, fast (less than 10 minutes), noninstrumental, and thus easily portable for use in the workplace.

Title of Project: Sustained-Action Nalmefene
Principal Investigator: E.S. Nuwayser, Ph.D.
Awardee Organization: BIOTEK, Inc.
21-C Olympia Avenue
Woburn, MA 01801
Telephone Number: (617) 938-0938
Awardee Number: 1 R43 DA04573-01

Nalmefene has been shown to be an effective pharmacological intervention for protecting postaddicts from re-addiction. With this modality, in contrast to methadone, the patient is free of opioids. The overall objective of this program during the next 3 years is to develop a sustained-action formulation of nalmefene that is effective for at least a month, and to file an Investigational New Drug (IND) application with the Food and Drug Administration.

Phase I will demonstrate the feasibility of the project. Injectable nalmefene microcapsules will be prepared and evaluated for *in vitro* drug release rates, drug content, surface morphology, and size distribution. The duration of action will be determined for promising formulations *in vivo* using several animal models.

Phase I studies will provide the methodological basis for further development of the formulation in Phase II. During Phase II, the prototype development will be completed, efficacy and safety tests will be conducted, and manufacturing procedures will be defined to support an IND application in anticipation of human trials.

Title of Project: Sustained-Release Naltrexone Microcapsules
Principal Investigator: Michael H. Gay, Ph.D.
Awardee Organization: BIOTEK, Inc.
21-C Olympia Avenue
Woburn, MA 01801
Telephone Number: (617) 938-0938
Awardee Number: 1 R43 DA04460-01

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The objective of this project is to develop sustained-action, injectable, biodegradable, naltrexone microcapsules to maintain plasma levels at 2 ng/ml for at least 1 month. Phase I support is sought for a 6-month period to conduct preliminary feasibility studies.

During Phase I, naltrexone microcapsules will be prepared using BIOTEK, Inc.'s air suspension process. This process produces true wall/reservoir microcapsules with zero order release characteristics. Microcapsules will be evaluated for *in vitro* release rates, surface morphology, drug content, and size distribution. The duration of antagonist release will be determined for several formulations and doses in rats using a simple observational screen test. The most promising formulation will be administered to rabbits so that plasma samples may be obtained during the time course of release. These samples will be provided to NIDA for analysis.

These Phase I studies will provide the basis for further development during Phase II when the final prototype formulation will be tested in a variety of animal models. Pharmacokinetic studies will be conducted and documentation will be prepared for an IND application.

Title of Project: Transdermal Nicotine—An Aid to Smoking Cessation
Principal Investigator: E. S. Nuwayser, Ph.D.
Awardee Organization: BIOTEK, Inc.
21-C Olympia Avenue
Woburn, MA 01801
Telephone Number: (617) 938-0938
Awardee Number: 1 R43 DA04572-01

Nicotine substitution or maintenance has been shown to be an effective aid for ceasing smoking. The overall goal of this program is to develop a transdermal nicotine delivery system as an aid to cessation of smoking based on BIOTEK, Inc.'s DermaPatch concept and system for preparing sustained-release preparations of liquid materials. This system, called NicoPatch, will be designed to deliver nicotine for at least 24 hours at a dose sufficient to maintain a blood nicotine level of about 20 ng/ml. In preliminary studies, sustained-release matrixes were produced and tested. A prototype vehicle has been shown to deliver nicotine transdermally *in vitro*.

The objective of the Phase I study is to demonstrate the feasibility of this system. Specifically, a sustained-release, nicotine DermaPatch matrix will be developed and characterized by *in vitro* drug-release rates. Utilizing nude mouse skin *in vitro*, transdermal diffusion of NicoPatch formulations will be evaluated. The rate of delivery of nicotine and the blood levels achieved will be estimated by *in vivo* studies in guinea pigs and rabbits.

During Phase II, further *in vitro* and *in vivo* testing will be required to optimize the formulation. Toxicology studies will be conducted and an Investigational New Drug application filed with the FDA. Based on these studies, industrial support will be sought for commercializing the system.

Title of Project: Development of a Methadone Maintenance Program Network
Principal Investigator: Leslie E. Cohen
Awardee Organization: Birch & Davis Associates, Inc.
8905 Fairview Road, Suite 300
Silver Spring, MD 20910
Telephone Number: (301) 589-6760
Awardee Number: 1 R43 DA04569-01

Birch & Davis Associates, Inc. will determine the feasibility of establishing a methadone maintenance treatment program network for traveling clients. All methadone programs located within the United States will be identified through contact with federal agencies (e.g., National Institute on Drug Abuse, Food and Drug Administration, Drug Enforcement Administration), state agencies, and other organizations with access to information on treatment programs. Once identified, each methadone treatment program will be contacted to ascertain program-identifying information (e.g., name, address, telephone number, fees) and interest in serving as a participating program in the proposed network. The outcome of Phase I will be a comprehensive directory of publicly and privately funded methadone maintenance programs and a listing of those that indicate interest in participating as a sending and/or receiving program in a treatment referral network.

The methadone program directory to be developed at the conclusion of Phase I will be used during Phase II to pilot-test the acceptability, effectiveness, and efficiency of a treatment program network that arranges client travel throughout the country. Phase II also will provide the opportunity to determine an appropriate fee schedule for nationwide implementation of the referral network during Phase III.

Title of Project: Development of a *Cannabis* Fingerprint
Principal Investigator: Mahmoud A. El Sohly, Ph.D.
Awardee Organization: El Sohly Laboratories, Inc.
1215½ Jackson Avenue
Oxford, MS 38655
Telephone Number: (601) 236-2609
Awardee Number: 1 R43 DA05396-01

This project intends to study the feasibility of developing analytical procedures to be used for identifying the country of origin of a given *Cannabis* sample on the basis of its chemical profile. Gas chromatography/mass spectrometry (GC/MS) will be the main technique used in the development of such procedures.

Both underivatized and derivatized *Cannabis* extracts from multiple samples from each country under consideration will be analyzed. High-resolution capillary columns will be used with programmed temperatures to maximize the number of chromatographic peaks to be used for developing each sample's fingerprint. In addition, high-resolution, high-performance liquid chromatography (HPLC) columns (3 µm particle size) will be examined either as a primary technique or as a backup procedure if needed. Data analysis will be by qualitative and quantitative comparison of the chromatographic characteristics of each sample. A database will be developed for future use in analyzing unknown samples.

Title of Project: Enhancement of the Addiction Severity Index
Principal Investigator: Grant R. Grissom, Ph.D.
Awardee Organization: Integra, Inc.
3910 Chestnut Street
Philadelphia, PA 19104
Telephone Number: (215) 662-4080
Awardee Number: 1 R43 DA05395-01

The overall project goal is to standardize the administration process and promote the appropriate use of the Addiction Severity Index (ASI) in substance-use treatment and research. The ASI is the most widely used structured clinical interview protocol in the field. When used by a trained technician, it has good reliability and validity, but it is vulnerable to misuse by untrained personnel.

Specific aims are to ensure that users are well trained and to enhance the usefulness of the ASI through: (1) production and dissemination of a videotape for use in training, (2) enhancement of the ASI Instruction Manual, (3) establishment of a process for testing and certifying ASI administrators, (4) development of a normative database, (5) establishment of ASI reliability and validity for various patient populations, (6) development of software for scoring the ASI and interpreting results, and (7) publication of a newsletter providing the user community with research findings and other information pertinent to the ASI. Achievement of these aims would provide an innovative product and service to the more than 600 sites worldwide that currently use the ASI and would encourage its further dissemination.

Title of Project: Interactive Video for Marijuana Use Prevention
Principal Investigator: Steven T. Bignell
Awardee Organization: Keneko Communications, Inc.
1700 Mission Street, Suite 203
P.O. Box 1830
Santa Cruz, CA 95061-1830
Telephone Number: (408) 429-9822
Awardee Number: 1 R43 DA04562-01

This project proposes to develop and evaluate an interactive, video-based curriculum (interactive video disk and/or tape and teacher curriculum) designed to prevent young adolescents aged 11 to 13 from using marijuana and to help them help their peers to refrain from marijuana use.

The students will participate in the interactive video by making decisions at key points in a problematic dramatized situation. Depending on the students' decisions, the video drama enables the viewers to see the effects of their judgments on the continuation and outcome of the drama. The goal is to help students identify the range of strategies for not using marijuana in social situations where peer pressure to use marijuana occurs and then to model those strategies. The interactive video curriculum will be used in a group setting, facilitated by a teacher or peer leader without the need for multiple sets of equipment.

Specific aims of Phase I are to determine the behavioral objectives and real-life scenarios related to marijuana-use behavior; to develop storyboards for the interactive video; to develop a curriculum framework outlining teaching activities; to select the interactive system with the best commercial value; to assess the strengths of likely markets; and to complete the selection of research sites for Phase II.

Title of Project: Nicotine Faders—Improved Method of Quitting Cigarettes
Principal Investigator: Leslie N. Aikman
Awardee Organization: Medical Dynamics International
1617 Westcliff Drive, #208
Newport Beach, CA 92660
Telephone Number: (714) 645-3700
Awardee Number: 1 R43 DA04571-01

The proposed research will establish the efficacy of nicotine-fading filters as an adjunct to smoking cessation. Smoking is a highly addictive behavior that leads to tremendous social costs in excess disease and disability. Techniques that can assist smokers to quit would have obvious health benefits. Nicotine faders represent a new technology designed to help smokers progres-

sively reduce nicotine intake. This can significantly facilitate the quitting process when integrated with additional smoking cessation strategies. Preliminary work strongly suggests that the filters substantially reduce smoke exposure (data have been obtained from both laboratory and clinical contexts). The filters also appear to overcome several serious problems associated with traditional brand-switching procedures.

A minimum of 60 subjects (6 groups) will be randomly assigned to either nicotine faders or brand switching. Groups will follow a smoking cessation clinic procedure. Recycling of initial relapsers will also be encouraged. It is hypothesized that nicotine faders will be significantly more effective than brand switching in producing reductions in levels of cotinine and carbon monoxide. If results are as hypothesized, a Phase II application will be prepared that combines nicotine faders with optimal self-help cessation approaches.

Title of Project: Specific Assays for Fentanyl Derivatives and Metabolites
Principal Investigator: Peter B. Dewhurst, Ph.D.
Awardee Organization: Microanalytic Research, Inc.
23461 Ridge Route, Unit H
Laguna Hills, CA 92653
Telephone Number: (714) 768-5419
Awardee Number: 1 R43 DA05377-01

The long-term objective of this project is the development of a rapid quantitative assay for fentanyl and a qualitative assay (screen) for fentanyl and other narcotics of the 4-anilinopiperidine series. The assay will be developed with the goal of measuring the drugs in whole blood spotted on filter paper, i.e., finger-stick assay. The proposed methodology will initially involve I^{125} immunoassay techniques, which will be changed later to a solid-phase enzyme immunoassay protocol.

The direct benefit to the health field will be the availability of a test that is rapid, nonlabor intensive, cost effective, and specific for the fentanyl family of drugs and detection of their abuse. The specimen employed can be obtained away from the laboratory by nontrained personnel and cannot be adulterated. Furthermore, it can be obtained without personal embarrassment to the individual being tested (e.g., being observed passing urine). The development of this test will make available to hospitals, doctors' offices, commercial laboratories, and drug-screening centers the first convenient, specific method for assaying or screening for the fentanyl family of drugs and their abuse.

Title of Project: Rapid Fiberoptic Fluoro-Immunoassay of Cannabinoids
Principal Investigator: Myron J. Block
Awardee Organization: ORD, Inc.
P.O. Box 50
Nahant, MA 01908
Telephone Number: (617) 592-3650
Awardee Number: 1 R43 DA04567-01

The project's long-term objective is to develop a very sensitive pocket-size fiberoptic fluoroimmunoassay (FIA) system for the detection of drugs of abuse. This detection will be either of individual drugs or simultaneously of 1 or more drugs in a panel of up to 50 drugs, and will take less than 30 seconds. Simultaneous detection will be done on a single specimen without any sample preparation or sample volume measurement.

There are two specific aims. The first is to determine the feasibility of ORD's FFIA method for the detection of cannabinoids. The proposed sensitivity goal is 10 ng/ml of the tetrahydrocannabinol (THC) urinary metabolite. Although an assay is proposed for urinary metabolites, ORD's method has the potential for measuring the free drug directly in a drop of whole blood without any separation steps. The second specific aim is to modify the FFIA instrument for an investigation into optimizing fiber area to allow for the maximum number of drugs to be detected simultaneously.

Title of Project: A Measure for the Effects of Drug and Alcohol Programs
Principal Investigator: Lorand B. Szalay, Ph.D.
Awardee Organization: Rapport
4528 49th Street, Northwest
Washington, DC 20016
Telephone Number: (301) 652-9020
Awardee Number: 1 R43 DA04713-01

The proposed research is directed toward the development of a measurement technology that can reliably and accurately indicate changes in client attitudes and perceptions that result from treatment. The instrument will be designed to: (1) identify the critical dimensions of change that are characteristic of the resocialization of successfully rehabilitated drug addicts; (2) measure the perceptual and motivational changes produced by treatment and the progress of resocialization along its critical dimensions and identify the critical elements in the treatment process; and (3) allow use of information about the client's perceptual and motivational dispositions and their changes to help therapeutic counseling take into account individual client dispositions that might otherwise be ignored.

Title of Project: A One-Step Colorimetric Immunoassay for Cannabinoids
Principal Investigator: Kenneth E. Rubenstein, Ph.D.
Awardee Organization: Whale Scientific, Inc.
4945 Monaco Street
Commerce City, CO 80022-4609
Telephone Number: (303) 289-4781
Awardee Number: 1 R43 DA04563-01

Pervasive abuse of marijuana has led to the widespread adoption of commercial tests to detect cannabinoids in urine at sites as diverse as military bases, police stations, and workplaces.

This project utilizes innovative immunochemical technology to fill the, as yet, unmet need for a cost-effective test that can be performed by unskilled personnel in nonlaboratory settings with no special instrumentation. It is proposed to pass urine through a column containing all the test materials. A color will develop in the detection zone of the column, the length of which is proportional to the concentration of cannabinoids in the urine.

The goal of Phase I is to prepare the materials to demonstrate technology feasibility. Then a cannabinoid assay will be assembled and its performance characteristics evaluated. In Phase II, the assay will be optimized for commercial acceptability and complete performance evaluations will then be completed.

Alcohol, Drug Abuse, and Mental Health Administration
National Institute on Drug Abuse

Phase II Grant

Title of Project: Supercritical Fluid Chromatography of Cannabinoids
Principal Investigator: Douglas W. Later, Ph.D.
Awardee Organization: Lee Scientific, Inc.
4426 South Century Drive
Salt Lake City, UT 84123
Telephone Number: (801) 261-2300
Awardee Number: 2 R44 DA04035-02

The analysis of metabolites in body fluids from users of *Cannabis* is often difficult due to the polarity and thermal instability of these compounds. Current methods, when applicable, require extensive sample preparation and highly trained personnel, and there may be some ambiguity in determination. This research is designed to expand the applicability of supercritical fluid chromatography to actual clinical specimens and to develop explicit analytical protocols for the analysis of the cannabinoid metabolites.

The development of these methods will include: (1) continued research into optimal detection systems, including the mass selective detector; (2) continued development of improved stationary phases and column technology, including the potential use of packed capillary and microbore columns; (3) the refinement and testing of a supercritical fluid extraction-supercritical fluid chromatography system; and (4) development and evaluation of analytical protocols for cannabinoids and related metabolites, including sensitivity, reproducibility, and recovery from actual clinical samples.

NATIONAL INSTITUTE OF MENTAL HEALTH

Phase I Grants

Title of Project: Preventing Working-Parent Stress
Principal Investigator: Julius H. Marlowe, Ph.D.
Awardee Organization: Northwest Family & School Consultants, Inc.
Box 11101, 575 West Broadway
Eugene, OR 97440
Telephone Number: (503) 485-2711
Awardee Number: 1 R43 MH42441-01

Phase I of this project is designed to produce and systematically evaluate a three-level media and computer-based "Family Facilitation" instruction program for working parents. The program will be further developed and tested during Phase II and ultimately marketed in the workplace through Employee Assistance Programs.

The main focus of the program is to reduce stress by helping working parents deal with the child-management problems that are a universal component of rearing children. It is argued that child-management problems increase parental stress at work, as well as in the home. The proposed program will reduce that stress. Problem behavior in early childhood that is not successfully dealt with has been shown to lead to a variety of mental health problems in adolescence and adulthood.

The program is adapted from two decades of clinical studies in the development and assessment of parent training and problem prevention strategies. As part of the Phase I project, an experiment will be conducted to assess the effectiveness of the program, the results of which will lead to refinements and expansion during Phase II.

Title of Project: Active Electrode Hat for EEG Imaging of Schizophrenics
Principal Investigator: Nelson H. Morgan, Ph.D.
Awardee Organization: SAM Technology, Inc.
1855 Folsom Street
San Francisco, CA 94103
Telephone Number: (415) 621-3999
Awardee Number: 1 R43 MH42725-01

The aim of the proposed work is to develop an active electrode hat for high-quality EEG recordings without skin preparation or electrolyte gels. This will greatly reduce patient preparation time for multichannel EEG recordings. It will also improve the signal quality over time, because there will be no electrolytic fluid to dry up.

Title of Project: A Digital Telemetry Monitor with Modular Features
Principal Investigator: Peter Brandenburg
Awardee Organization: United States Control Systems Corporation
502 Palm Street, #5
West Palm Beach, FL 33401
Telephone Number: (305) 659-4327
Awardee Number: 1 R43 MH41367-01A1

This program develops a modular short-range radio telemetry system to monitor independent real-time physiological parameters on unrestrained subjects. The system transmits data

in coded digital form to improve its immunity to radio-channel noise and signal dropouts. The radio receiver connects to a personal computer to permit the use of a wide variety of inexpensive data display and storage devices. The transmitter's measurement setup values and programs are loaded via menu selections on the personal computer so that computer expertise is not needed to run standard experimental procedures. Users may also write custom programs in popular high-level languages.

The microprocessor-based transmitter accepts eight plug-in modules that contain physiological measurement circuits and special system features. The modules are standardized so that any combination of different module types can be used in the transmitter. Initially, eight types of modules will be developed to support psychophysiological studies of infants and children in situations where long-term monitoring is not currently practical. An open system architecture will encourage other investigators and third-party vendors to develop additional modules and software.

Phase II Grants

Title of Project: Wrist Activity Monitoring for Outpatient Behavior
Principal Investigator: William Gruen
Awardee Organization: Ambulatory Monitoring Inc.
731 Saw Mill River Road
Ardsley NY 10502
Telephone Number: (914) 693-9240
Awardee Number: 2 R44 MH39880-02A1

Phase I of this program produced two commercially feasible human activity monitoring systems that are now ready for clinical trial. The unit selected for Phase II evaluation uses a microcomputer, weighs 3 ounces, stores 16,000 words, and has a movement sensitivity of 0.01 gram. High sensitivity to motion is combined with artifact rejection and is programmable for various epoch lengths.

Two sleep research centers have agreed to add actigraphy to their research on insomnia and sleep apnea. Data will be centrally archived and used to develop computer programs for analyzing data. Programs to measure sleep length, sleep latency, sleep fragmentation, and apneic movement will be developed. Actigraphically derived measures will be compared with standard polysomnographic indices.

Approximately 15 percent of the population experiences sleep disturbances; current diagnostic procedures are labor and facility intensive. Actigraphy has demonstrated potential as a low-cost diagnostic screening tool and case management adjunct to current practices. Data are collected on an outpatient basis in the patient's own environment and the technology is suitable for establishment of scanning services similar to those used in cardiac care. Objective measurement of motor activity has promise for application in neurology and psychiatry.

Title of Project: An Image Preparation and Presentation System for Psychobiology
Principal Investigator: William C. Bradley, Ph.D.
Awardee Organization: American Innovision, Inc.
7750 Dagget Street, Suite 210
San Diego, CA 92111
Telephone Number: (619) 560-9355
Awardee Number: 2 R44 MH41362-02

New technology developed under Phase I of this project makes possible an inexpensive image preparation system to allow a researcher who is not an experienced video editor to produce a wide variety of images for use as stimuli in many areas of psychobiology. The system would allow researchers to compose images by combining stored images of the real world with elements

created by computer graphics. A sophisticated video mixer would permit the user to determine on a pixel-by-pixel basis which image fractions should overlay the background or to specify that overlaid and background pixels should be mixed to achieve complex transparency and blending effects. The system would let a researcher build a library of images from live camera scenes, photographs, and computer graphics, and compose stimuli by excising parts of images, moving them around in real time, and overlaying or blending them with a background as necessary.

Title of Project: Noninvasive Imaging of Regional Brain Blood Flow
Principal Investigator: James P. O'Halloran, Ph.D.
Awardee Organization: BioComp Systems, Inc.
6399 Wilshire Boulevard, Suite 900
Los Angeles, CA 90048
Telephone Number: (213) 933-9451
Awardee Number: 2 R44 MH41041-02

In Phase II, BioComp Systems, Inc. proposes to develop a new functional brain-imaging modality based on electrical impedance data provided by noninvasive, nonradiological rheoencephalographic (REG) technology. Tetrapolar REG impresses a small (1mA), high-frequency (100 Khz) field across the patient's head to derive region-specific, intracranial pulse-volume waveforms (ΔZ) as well as total impedance (Z_o) parameters.

A bimodal approach to REG imaging will be taken. In Method 1, a linear interpolation algorithm, developed at NIMH, will be used; it assumes equal area projection of cortical-scalp voltage values. Method 2 estimates cortical voltage values through a deconvolution-interpolation procedure requiring estimation of cortical current densities using a previously developed 4-sphere model of the head. Evaluation and refinement of these algorithms will be based on statistical comparisons with simultaneously collected Xe^{133} data. The imaging process will then be field tested in patients with (1) NMR-confirmed focal cortical infarction (n=15); (2) NMR-confirmed focal cortical tumors (n=15); and (3) schizophrenics (n=10) and normal subjects (n=10). Schizophrenic patients and matched control subjects will be studied both at rest and during the performance of a cognitive task that induces differential cortical blood flow patterns. Impedance-based hemispheric blood flow patterns will be compared with simultaneously conducted single photon emission computed tomography (SPECT) blood flow patterns.

Title of Project: An Automated Phone System for Health-Promotion Programs
Principal Investigator: Marc D. Schwartz, M.D.
Awardee Organization: Computers in Psychiatry/Psychology, Inc.
26 Trumbull Street
New Haven, CT 06510
Telephone Number: (203) 562-9873
Awardee Number: 2 R44 MH41622-02A1

Lifestyle habits are a factor in the major causes of death and disability in the United States. Traditional health-promotion (HP) interventions aimed at changing these habits have been least effective in tracking clients, maintaining the effects of the interventions over time, and providing information about outcome. This is because, in part, carrying out these tasks demands so much staff time.

In Phase I, a talking computer system, CATER, was developed that largely automates these functions. CATER periodically telephones HP-program participants, asks them questions (by digitized voice) about their compliance with medical treatments prescribed, decodes their touch-toned answers, branches appropriately, reminds and encourages subjects to comply with their treatments, and keeps records of these transactions.

In Phase II, it is proposed to study how well CATER enhances compliance with treatments prescribed for a group of hypertensive employees at a health maintenance organization. It will

re-contact them to ask about the specific treatments recommended for them, then periodically call to encourage and remind them about doctors' appointments, prescribed medication, and recommended changes in lifestyle. Over a 15-month period, CATER's effectiveness will be compared with a previously developed tracking system. Outcome measures will include changes in subjects' blood pressure and compliance with recommended treatments.

Title of Project: Updating the Tryon Multivariate Analysis Computer System
Principal Investigator: Robert B. Dean, Ph.D.
Awardee Organization: d^2 Associates
2555 North Clark, Suite 1703
Chicago, IL 60614
Telephone Number: (312) 477-4544
Awardee Number: 2 R44 MH38975-02

The long-term objective of this project is to update, enhance, and commercially distribute two computer programs that implement the unique multivariate analysis techniques developed during the 1960s. One main goal is to produce an enhanced Fortran 77 version of the main Tryon system (TRYSYS), portable across all mainframe computers. A second goal is to refine and greatly expand a new Fortran program (TRYCLUS) specifically designed for maximum portability and enhanced user-friendliness.

Tryon multivariate analysis techniques are especially useful for the following biomedical research tasks: analysis of the dimensionality of assessment inventories; construction of reliable assessment scales from large item pools; comparison of factor structures across diverse clinical groups; development of clinical taxonomies, produced by clustering cases in a multidimensional space defined by reliable assessment scales; and Monte Carlo prediction of important outcome or criterion variables from taxonomic group membership.

TRYSYS work will focus on systematically updating the code so that it is written completely in Fortran 77 and is parameterized, for ease in adjusting the size of datasets permitted to the amount of computer memory available. TRYCLUS work will focus on adding additional data processing and statistical analysis techniques and further enhancing its user-friendliness, especially in the microcomputer environment.

Title of Project: Computer-Directed Interactive Communication
Principal Investigator: Curt A. Knoppel
Awardee Organization: ITX Laboratories, Ltd.
11620 Killion Street
North Hollywood, CA 91601
Telephone Number: (818) 762-7672
Awardee Number: 2 R44 MH41665-02

In Phase II, ITX Laboratories, Ltd. expects to conclusively demonstrate the merits of its "STIM" tutorial system for special education and to have it ready for marketing.

In an interactive video disk format, a sample of the "extended skills curriculum," developed by the Los Angeles Unified School District and used in its special education division since 1981, provided the Phase I base for investigations. The three major curriculum portions (reading, language, and mathematics) will be converted to video-disk-based courseware for use as "teacher's aides" for handicapped children, with emphasis on disorders such as autism, aphasia, and learning handicaps.

The high degree of hardware sophistication required has been demonstrated in a prototype workstation still in use for continued classroom evaluation. A computer-controlled touchscreen is used by children to register their responses to

tasks presented on dual and independent color monitors receiving audio-visual still and moving programming from double video disk drives, each with 54,000 individually accessible video frames. An onboard video camera, with VCR, provides a live video tape-record that combines with computerized scorekeeping of right-wrong responses and response time. Vital hardware refinements and features, suggested in Phase I research, will be explored and implemented during Phase II. ITX Laboratories, Inc. expects to market STIM as a hardware-courseware subscription service.

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PUBLIC HEALTH SERVICE

CENTERS FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Phase I Grant

Title of Project:	Audio Mechanical Transducer Communication System
Principal Investigator:	Hugh R. Cameron
Awardee Organization:	Camtech, Inc. 11903 Welland Drive, Suite G Indianapolis, IN 46229
Telephone Number:	(317) 894-1310
Awardee Number:	1 R43 OH02313-01A1

The Audio Mechanical Transducer (AMT) Communication System will significantly improve the environment of workers in high-ambient-noise conditions by providing a new method of communicating. The system will attach directly to most forms of hearing protection without modification of the protector. It will be low cost, permit multiple audio inputs, and demonstrate man/machine interface capabilities. The system will have benefits to both management and workers.

There are approximately 2.9 million individuals in the United States working in a high-noise environment. Lack of communication can cause feelings of isolation and reduce the effectiveness of hearing protection programs. The inability to hear warning signals clearly has led to injuries and deaths. The majority of workers in high-noise environments do not benefit from existing communication systems. The AMT Communication System addresses each of these areas.

Hearing protection programs have traditionally been based on the admonition, "wear hearing protection or you will go deaf." The AMT Communication System will present an alternative: "wear hearing protection and enhance your work environment."

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PUBLIC HEALTH SERVICE

Office of The Assistant Secretary for Health

NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

Phase II Contract

Title of Project: Computer-Based Health Education for Teenagers: Health-Risk Game

Principal Investigator: Ben T. Williams, M.D.
Awardee Organization: University Park Pathology Associates, P.C.
1408 West University Avenue
Urbana, IL 61801
Telephone Number: (217) 337-4700
Awardee Number: 282-87-0026

University Park Pathology Associates, P.C. intends to program and evaluate a computer game for use in health-education classes at the secondary school level or for use on inexpensive home computers. The three-part game, designed during Phase I, incorporates mortality risks and risks attributable to health-behavior choices in 17 successive frames, each representing a 5-year period for ages 15 through 100. Concepts of average and attributable risk for various health habits will be displayed through the medium of a fast-paced game. Beta-testing of the educational software will take place in local health-education classrooms. The games will be marketed to school health educators and to the general public.

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Phase I Grants

Title of Project: A Guidebook and Training Materials for Medicare HMO Broker Organizations
Principal Investigator: Stuart P. Hanson
Awardee Organization: Berkeley Planning Associates
3200 Adeline Street
Berkeley, CA 94703
Telephone Number: (415) 652-0999
Awardee Number: 500-87-0025

This Phase I research seeks to demonstrate the feasibility of developing guidebooks, training materials, and computer software templates to assist potential broker organizations in becoming effective facilitators of informed decision making among Medicare beneficiaries when it comes to choosing among competing HMO and CMP risk programs. These materials will focus on helping brokers understand: (1) why Medicare beneficiaries enroll in, do not enroll in, or disenroll from risk programs; (2) how the competitive HMO market functions; (3) how HMOs identify, attract, and maintain satisfaction among Medicare-eligible enrollees; (4) how to obtain access to lists of Medicare eligibles and grievance reports from the Health Care Financing Administration within a given geographic area; and (5) how to develop standard practice guidelines designed to ensure the integrity of the services brokers provide to Medicare beneficiaries.

To achieve these objectives, Berkeley Planning Associates will consult with a limited number of experts and consumers to validate the basic content of a draft outline of a guidebook and seminar curriculum, as well as the basic specifications of software templates to assist the consumer in selecting an appropriate HMO and assist the broker in monitoring consumer satisfaction.

Title of Project: A Guidebook to Assist State Medicaid Programs
Principal Investigator: Herbert M. Birch, Jr.
Awardee Organization: Birch & Davis Associates, Inc.
8905 Fairview Road, Suite 300
Silver Spring, MD 20910
Telephone Number: (301) 589-6760
Awardee Number: 500-87-0022

The objective of this project is to develop a guidebook to assist state Medicaid programs in contracting with and monitoring prepaid providers. In Phase I, a detailed outline of the guide will be prepared through collection of existing materials, input from two visits to selected Medicaid programs, and the use of a prepayment/Medicaid expert panel for topic suggestions and product review.

Title of Project: Development of a Capitation Manual for State Medicaid Programs
Principal Investigator: Zachary Dyckman
Awardee Organization: Center for Health Policy Studies
6310 Steven's Forest Road, Suite 100
Columbia, MD 21046
Telephone Number: (301) 381-4203
Awardee Number: 500-87-0021

The primary purpose of this project is to develop a practical manual for the planning, design, and implementation of Medicaid Alternative Delivery System (ADS) programs. State Medicaid program experiences with health maintenance organizations and other ADS programs have been mixed, with some states achieving their cost, quality of care, and access objectives and others not. States have sometimes underestimated the complexity of the design and implementation requirements and overestimated cost savings achieved under the programs. This manual will help states that are considering ADS approaches learn from the experiences and mistakes of others and develop realistic ADS strategies and expectations.

The primary project tasks are: a review of the literature on Medicaid capitation experiences; interviews with recognized experts and with those involved in Medicaid ADS program implementation; and preparation of a clear, comprehensive manual for planning, design, and implementation of Medicaid ADS initiatives.

During Phase II, the Center for Health Policy Studies will provide training seminars for individual states or groups of states on Medicaid ADS program implementation. These seminars will cover the entire planning, design, and implementation process as well as focus on specific critical tasks.

Title of Project: Selecting and Administering Alternative Health Plan Options
Principal Investigator: Leonard Greenberg
Awardee Organization: Mandex, Inc.
8003 Forbes Place
Springfield, VA 22151
Telephone Number: (703) 321-0200
Awardee Number: 500-87-0024

Small business employers are often reluctant to offer their employees comprehensive health benefits because of the costs and administrative expenses attendant to the traditional indemnification mode of health insurance. The purpose of this research is to produce a guide that will advise small business employers of alternative options, such as health maintenance organizations, and of contractual arrangements, such as preferred-provider organizations; these could make health insurance more affordable and less administratively cumbersome. In addition to a detailed discussion of alternative modes of coverage, the guide will suggest factors that may be helpful in making an appropriate choice.

Increased competition and innovation are expected to bring about changes in the health care marketplace. Some organizational models will disappear; others will adapt. The guide concludes by discussing anticipated changes which may effect the small business employer's future choices. Bibliographic references and suggested additional sources of information are appended.

Title of Project: Automated Monitoring for HMO Quality Assessment
Principal Investigator: Donald F. Schaller, M.D.
Awardee Organization: Schaller Associates, Inc.
3200 North Central, Suite 680
Phoenix, AZ 85012
Telephone Number: (602) 265-2203
Awardee Number: 500-87-0023

Schaller Associates, Inc.'s long-term objective is to implement an effective, automated, quality monitoring program for health maintenance organization (HMO) administrators. The program will generate reports on profiles of care, identify exceptions to norms, be portable to alternative HMO settings, be usable by nursing and support staff, and will have a significant and lasting impact on quality assessment procedures in the HMO industry.

Phase I will produce a field-tested plan describing the minimum set of data elements re-

quired, their specific sources, and the relevant instruments, procedures, and resulting reports. Components of the system will include an encounter data system, a member information system, grievance/complaint and client-advocate systems, and health outcomes protocol. A technical advisory committee will assist in developing the plan, which will then be field tested at three sites, including a group, an IPA, and a staff-model HMO.

Phase I will provide a feasibility-tested foundation for Phase II development of computer software and documentation, hands-on implementation at selected HMO test sites, and efforts to insure acceptance of the program throughout the HMO industry. Schaller Associates, Inc. will then market the product commercially and provide user support.

Phase II Grants

Title of Project: Evaluating ICU Care, Quality Assurance, Efficiency, and Resource Utilization
Principal Investigator: Lawrence M. Rudner, Ph.D.
Awardee Organization: LMP Associates, Inc.
3109 Rolling Road
Chevy Chase, MD 20015
Telephone Number: (301) 986-1531
Awardee Number: 500-86-0031

Conceptual developments in the areas of illness-severity quantification, intensive care unit (ICU) efficiency, and quality assurance enable models of physiologic stability and therapeutic intervention to aid in ICU management and patient care. By combining specialized hardware, custom software, and statistical information based on the existing wealth of research, an easy-to-use, microcomputer-based system will be developed to enable ICU directors and physicians to evaluate and document the status of individual patients and measure and monitor the quality and quantity of rendered ICU care.

Prior research has demonstrated the feasibility of this project. By using bar-code methodology, LMP Associates, Inc. has overcome the thorny problem of data collection and entry. Analysis routines will make it possible to compute the wide range of complex statistics required by the models.

Building on prior research, this project will involve validating routines, providing data analysis options, expanding the system to include large numbers of patients and patient days, developing a manual, field testing the system, and preparing the system for commercialization.

Title of Project: QUEST II: Quality Assurance Expert System Testbed
Principal Investigator: Elena V. Torres
Awardee Organization: Meridian Corporation
4300 King Street, Suite 400
Alexandria, VA 22302
Telephone Number: (703) 998-3600
Awardee Number: 500-86-0032

The Phase II research for QUEST (an acronym for quality assurance expert system testbed) will expand the scope and functionality of Phase I, and leverage the Phase I results by using them with the Phase II results as a front end to the related project, NESTOR (nosocomial expert system testbed for original research).

While Phase I dealt with inferentially determining the occurrence of nosocomial (hospital-acquired) infections that were caused by *Enterobacteriaceae* and that resulted in either nosocomial urinary tract infections or nosocomial pneumonia, Phase II will expand to other bacterial agents (such as *Pseudomonas*), other non-

bacterial agents (such as *Rickettsia*, *Chlamydia*, spirochetes, fungi, and protozoa), and other kinds of infection (such as surgical wound, cutaneous, and bacteremia).

Phase II will operate in two modes, single patient and multiple patient. The single-patient mode will diagnose the presence of nosocomial infections in individuals, while the multiple-patient mode will diagnose infection trends by type of infection (such as urinary tract infections, lower respiratory, and surgical wound) or by service performed (such as internal medicine, surgery, and obstetrics. Blind tests and hospital trials will be run. The potential for commercial development of the system is significant.

Phase II Cooperative Agreements

Title of Project: Accessory Apartments—Developing a Private Partnership to Market the Concept and Counsel the Homeowner
Principal Investigator: Margaret Haske
Awardee Organization: Patrick H. Hare Planning and Design
1707 P Street, Northwest
Washington, DC 20036
Telephone Number: (202) 234-1219
Awardee Number: 90-AM-0183/02

The purpose of this project is the development of seminars on partnerships to install accessory apartments. Accessory apartments are installed in the surplus space of single family homes, typically by older homeowners. The homeowners are provided income, security, companionship, and services in return for rent reductions. Relatively few new apartments have been installed, however, even after permitting ordinances have been passed. The primary problem has been a lack of marketing to homeowners, and of help with the problems of installation.

This project is developing a seminar that shows remodelers, lenders, and real estate agents how to form partnerships to market accessory apartments. The seminars, which will typically be sponsored by local agencies, will allow these agencies to offer private sector businesses a business opportunity in which they can profit by helping people. The sponsors will be able to recover the seminar costs from registration fees.

Title of Project: Franchising Family (Home) Care
Principal Investigator: Gene Kane
Awardee Organization: Transferability, Inc.
256 South Monaco Parkway
Denver, CO 80224
Telephone Number: (303) 394-2525
Awardee Number: 90-PD-0128/02

Work under Phase I has included: (1) development of the econometric model of an operating franchise; (2) review of the "state of the system" and typical problems confronting family day care providers and the agencies seeking to promote quality family day care; (3) development of a prototype toy chest containing a variety of educational games and toys appropriate for various states of early childhood development and skills acquisition; and (4) outlines of some of the manuals necessary for program operation. The roles and activities for a national franchise structure have also been delineated.

Phase II activities will include detailed preparation, with an eye to quality and clarity, of the documentation and technical assistance materials that the system will require. Economic analysis indicates that only careful planning and administration of a local franchise will permit the operation to attain self-sufficiency and reasonable levels of stability. This makes the need for conscientious support from the national cosponsoring agencies very critical during the franchise operation. Thus, considerable time will be spent drafting, reviewing, and revising the written manuals and computerized accounting packages that will be made available to local franchise operators, national cosponsoring agencies, and any technical assistance sources.

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